Chronic Obstructive Pulmonary Disease (COPD)

Acknowledgment and Disclaimer
MEDICINE THROUGH THE GLASS SLIDE
is a free educational platform, an offering shaped by personal experience, informed by scientific literature and enriched by publicly available knowledge.

We walk in the light cast by giants, visionaries whose tireless pursuit of truth has illuminated the intricate beauty of medicine and microscopy.

This work pays homage to the researchers clinicians and educators whose insights form the bedrock of our understanding. Each image, each reflection echoes their enduring legacy.
All sources are acknowledged with gratitude and intellectual contributions are credited with full respect for legal and ethical standards.

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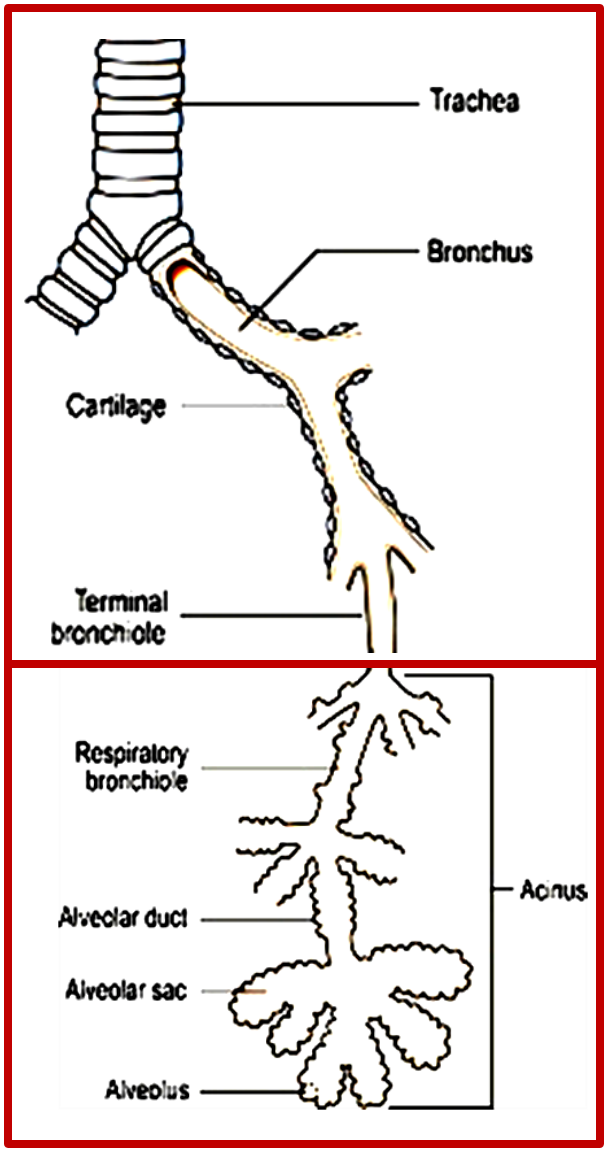
Respiratory system



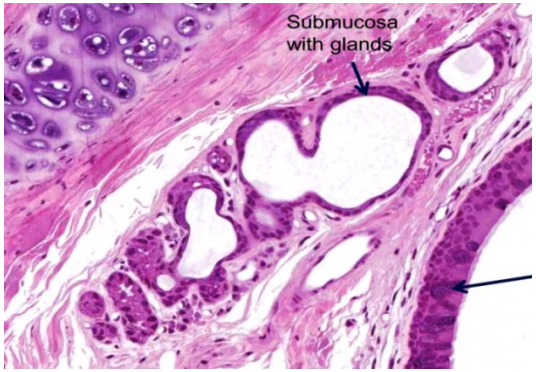
Histology

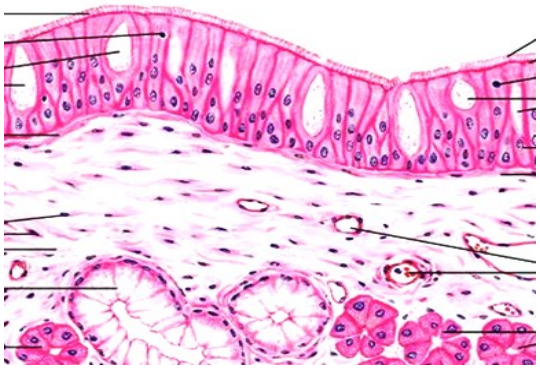
Trachea, bronchi and bronchioles are lined by respiratory epithelium (**pseudostratified ciliated columnar epithelium with goblet cells**)

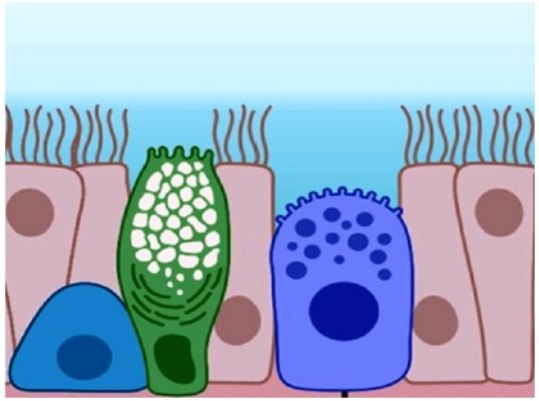
Trachea and bronchi have **cartilage and mucous glands** in their walls

Bronchioles have **mucous glands but no cartilage**

Pathology in this part of the respiratory system cause obstruction and called **obstructive lung disease**



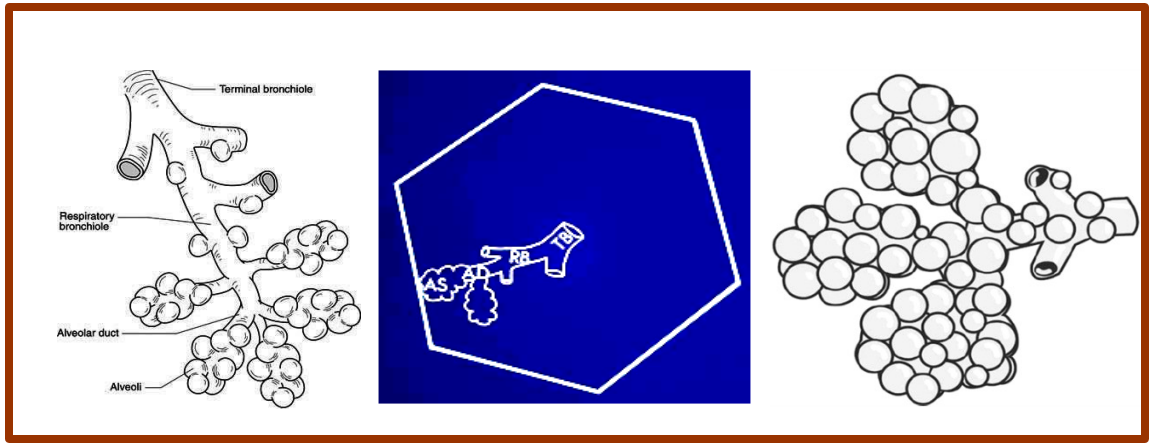




Acinus and lobule (lung parenchyma)

Acinus

5 mm unit of the lung distal to the terminal bronchiole
Consists of respiratory bronchiole, alveolar ducts and alveolar sacs
Called Primary lobule on imaging



Acinus (Primary Lobule)

Lobule

Up to 20 mm unit of lung, consists of a cluster of 3 to 5 acini
Called secondary lobule on imaging

Lobule (secondary Lobule)

Lobules are the smallest visible units on HRCT imaging (secondary lobules)

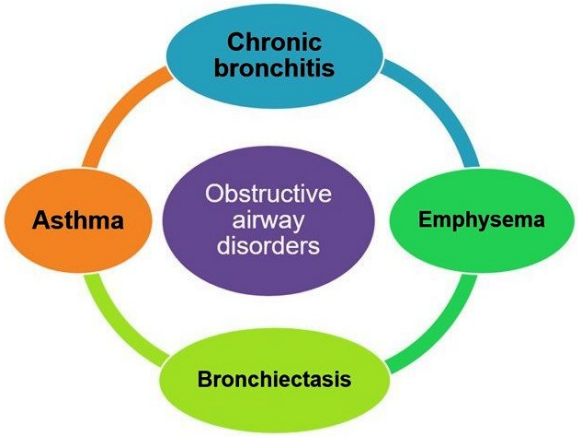
Acinus
Lung tissue, distal to the terminal bronchiole 5 mm in diameter

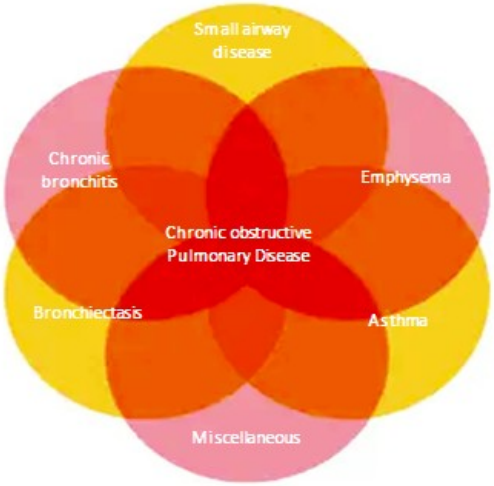
Lobule
Lung tissue 10 mm to 20 mm in diameter
Consists of 3 to 5 acini

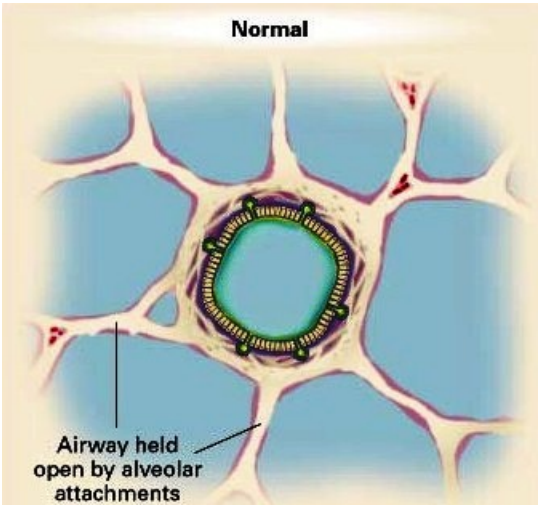
Lobules are the smallest visible units on HRCT imaging (secondary lobules)

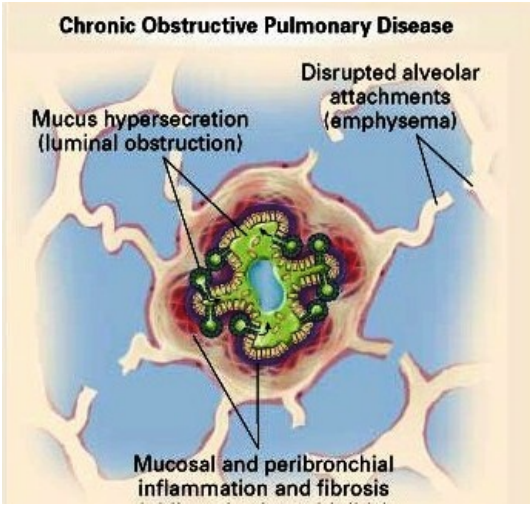
Functional (clinical) classification of lung diseases		
	Obstructive lung diseases	Restrictive lung diseases
Mechanism	Reduced airflow during exhalation due to airway obstruction or loss of lung tissue elasticity Pulmonary function tests show reduced expiratory flow rates	Decrease in the total lung volume, making it difficult to fully expand when inhaling Pulmonary function tests show reduced lung volumes and capacities
Location of disease	Mainly in air conducting units (bronchi and bronchioles) but sometimes in lung parenchyma	Distal gas exchanging units (lung parenchyma)
Examples	Chronic bronchitis Emphysema Asthma Bronchiectasis Small airways disease	Interstitial lung diseases Sarcoidosis Obesity Chest wall and other diseases

Obstructive lung diseases








Chronic Obstructive Pulmonary Disease
Disrupted alveolar attachments (emphysema)
Mucus hypersecretion (luminal obstruction)
Mucosal and peribronchial inflammation and fibrosis

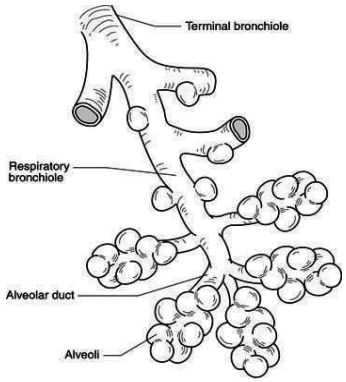
The main findings are **mural thickening, luminal narrowing increased mucus secretion, inflammation**

Divisions between these entities are not perfect and many patients have diseases with **overlapping features**

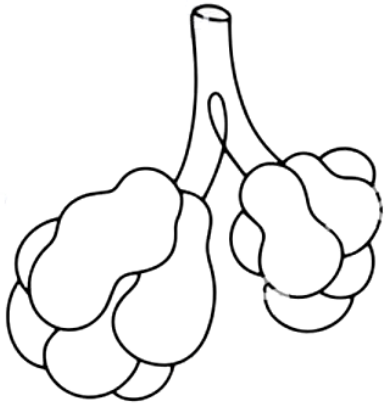
Chronic bronchitis and emphysema (COPD)
Asthma-COPD Overlap Syndrome (ACOS)
Bronchiectasis-COPD Overlap Syndrome (BCOS)

Chronic obstructive pulmonary disease				
Clinical term	Main site	Main pathology	Etiology	Manifestations
Emphysema	Acinus	Airspace enlargement Alveolar wall destruction	Smoking	Dyspnea
Chronic bronchitis	Bronchus	Mucous gland hyperplasia Hypersecretion Inflammation	Smoking Air pollutants	Cough Sputum
Asthma	Bronchus	Muscle hypertrophy, excess mucus secretion and inflammation	Immunological and other causes	Episodic cough Wheezing Dyspnea
Bronchiectasis	Bronchus	Airway dilatation and scarring and inflammation	Persistent infection	Cough Sputum Fever
Small airway disease	Bronchiole	Inflammation, scarring and airway obliteration	Smoking Air pollutants	Cough Dyspnea

Normal



Emphysema



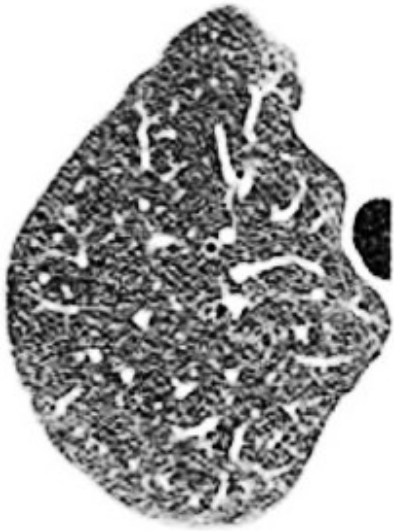
Emphysema

Abnormal permanent enlargement and destruction of small (<2mm) airspaces distal to the terminal bronchiole

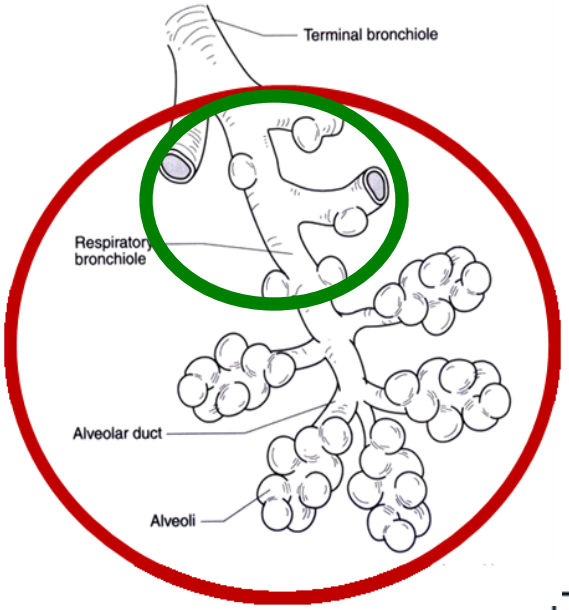
Digestion and loss of alveolar elastic tissue by **neutrophil elastase** causing respiratory bronchiole to collapse during expiration, resulting in **functional obstruction**

Persistent mild inflammation causes bronchiolar wall **fibrosis and muscle hypertrophy**, amplifying the airway obstruction

Normal

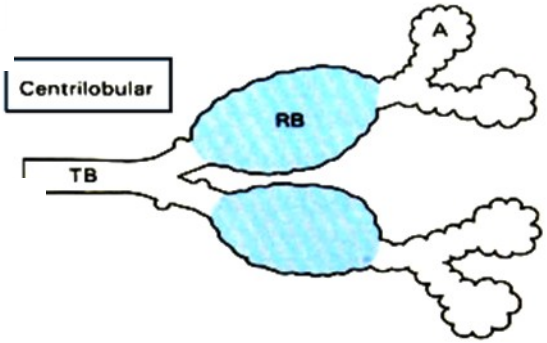


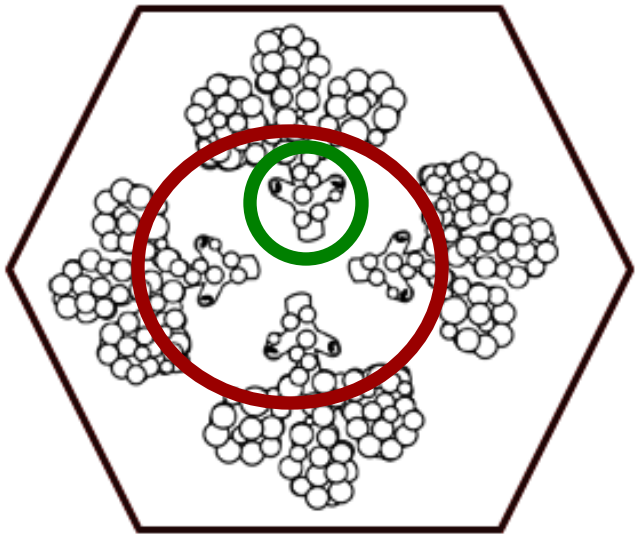
Emphysema



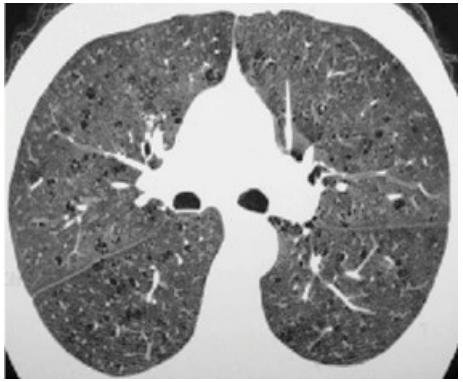
Proximal acinar

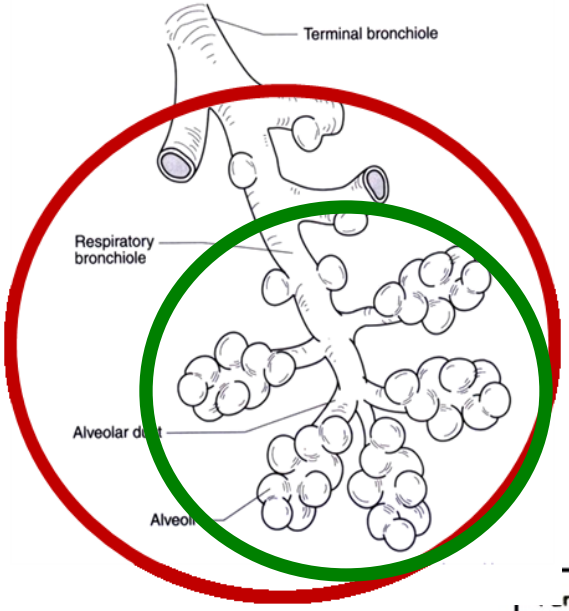
Centrilobular emphysema





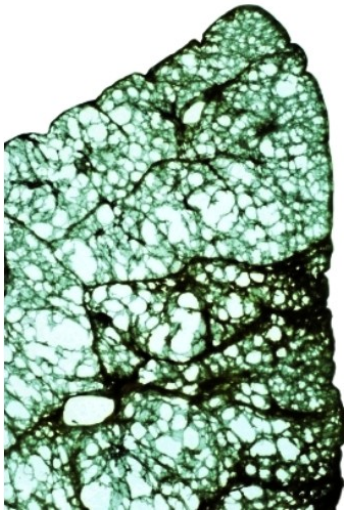
Centrilobular

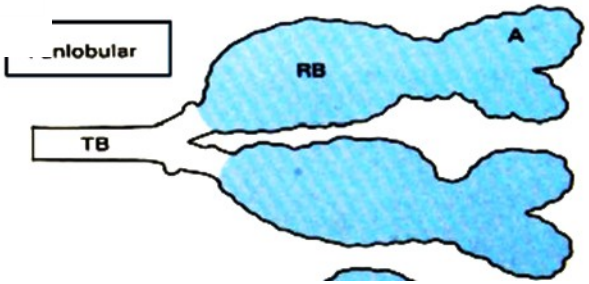


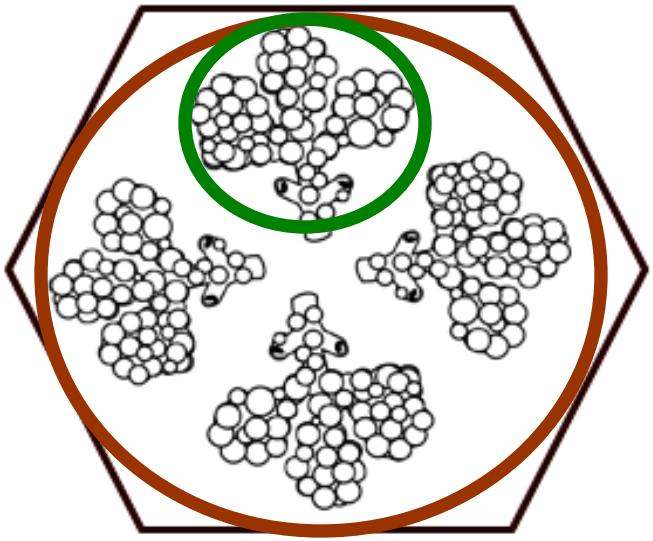


Panacinar

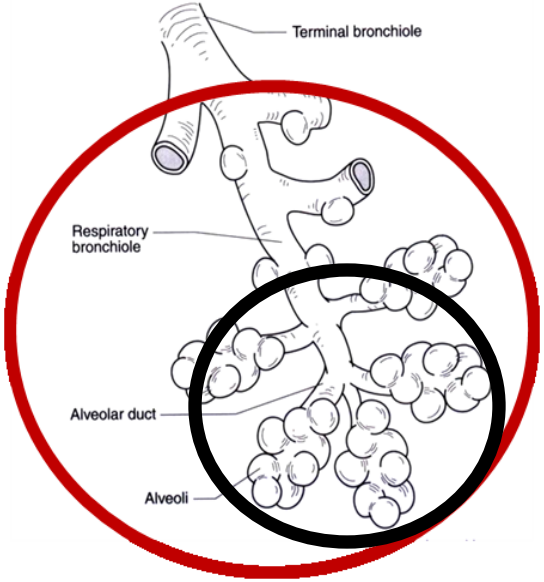
Panlobular emphysema



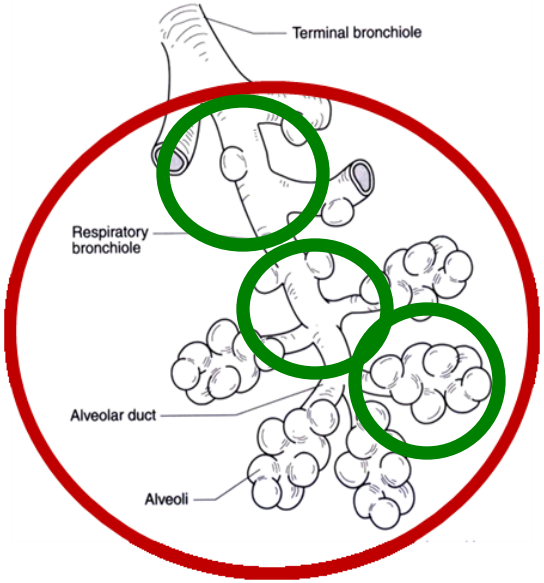




Panlobular

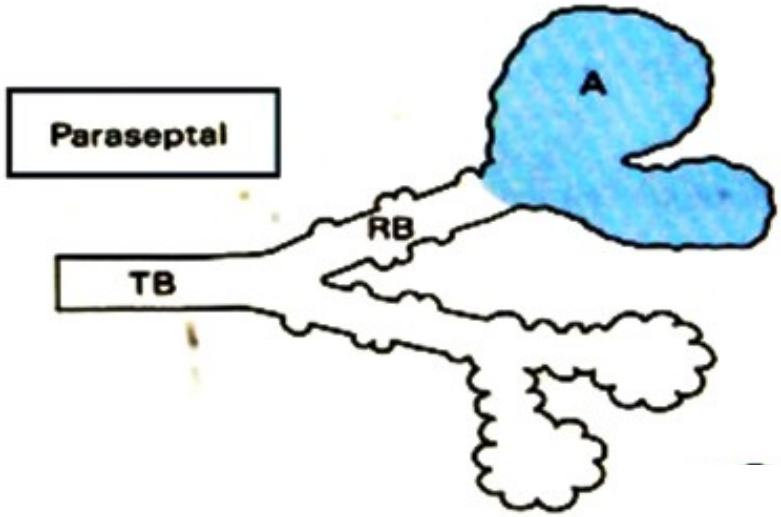


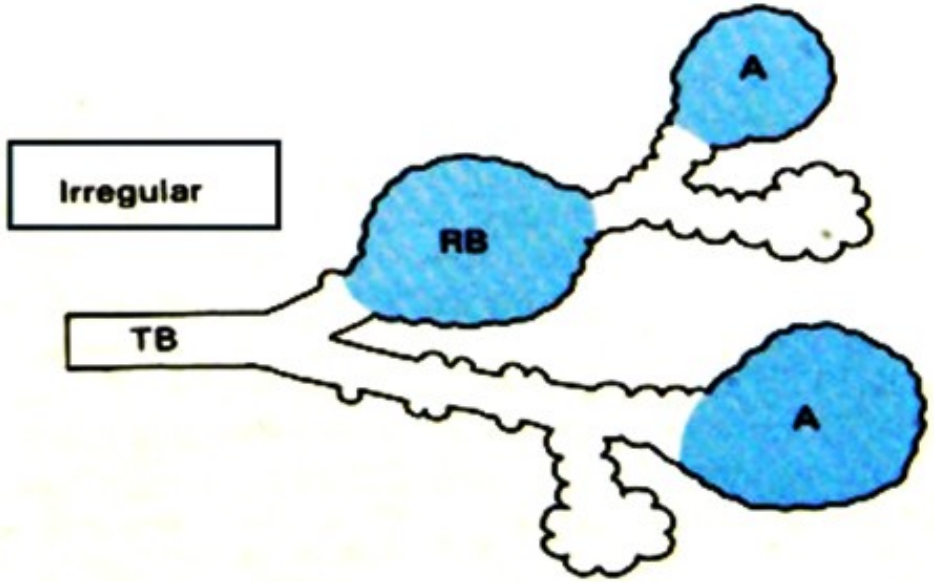
Distal acinar



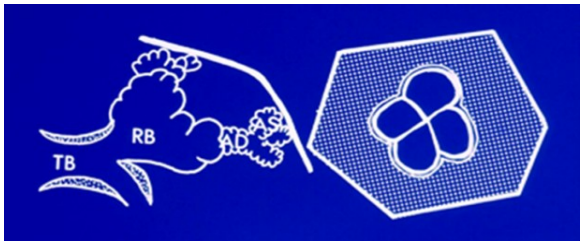
Irregular

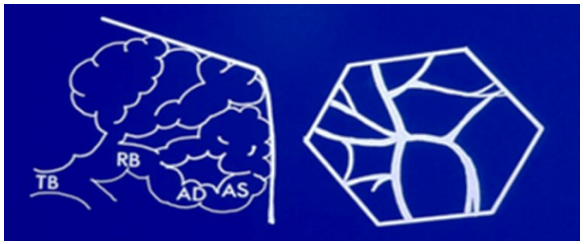
Distal acinar and irregular emphysema



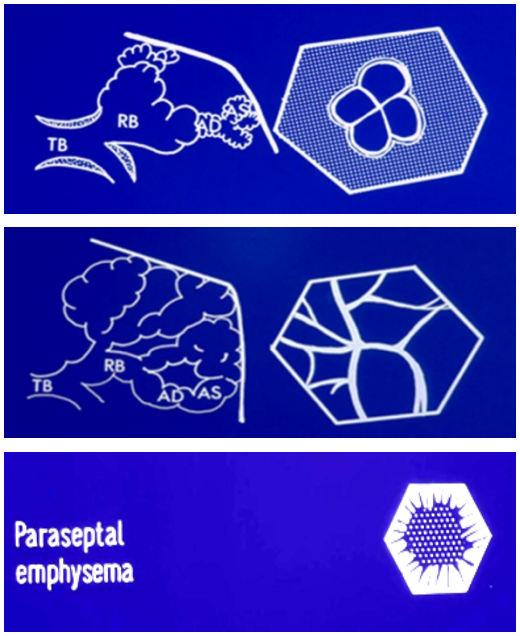


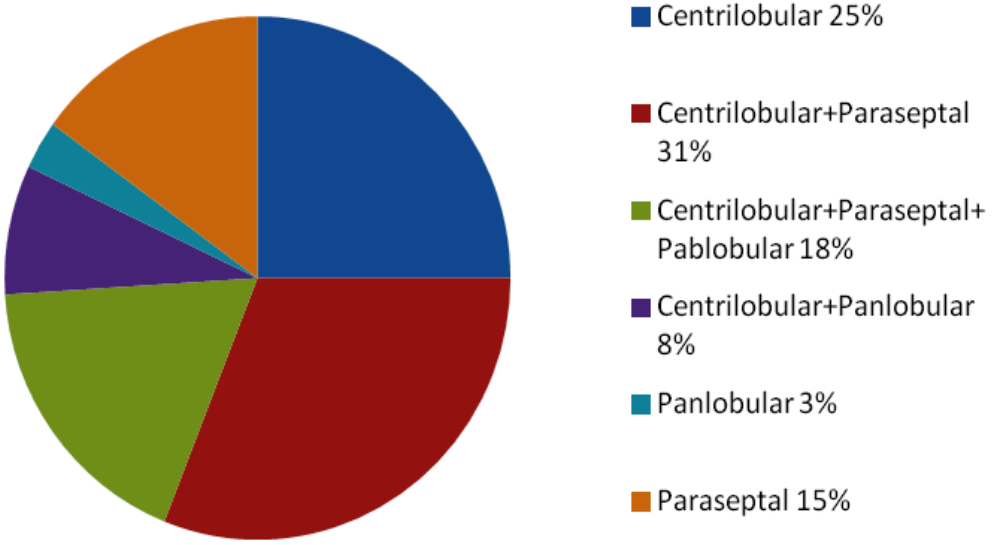
Emphysema classification	
Centrilobular Emphysema	**Most common** and clinically significant Occurs **heavy smokers** Destruction and enlargement of the **proximal parts of the acinus (respiratory bronchioles)** in **upper lobes and apices**
Panlobular emphysema	**Less common, occurs mainly in patients with α1-antitrypsin deficiency** Uniform destruction and enlargement of the **entire acinus in lower basal zones**
Paraseptal (distal acinar) emphysema	**Distal acinus** near the edge of the lobule and pleura and adjacent to **scars** **Spontaneous pneumothorax**
Irregular emphysema	**Irregular acinar involvement**, associated with **scarring.** **Asymptomatic and clinically insignificant**
Bullous emphysema	**Air-filled space of 1 cm** in diameter within the lung Result of **emphysematous destruction**





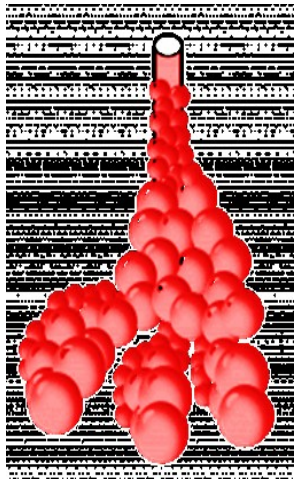
Normal | Centrilobular 52% | Paraseptal 33% | Panlobular 15%





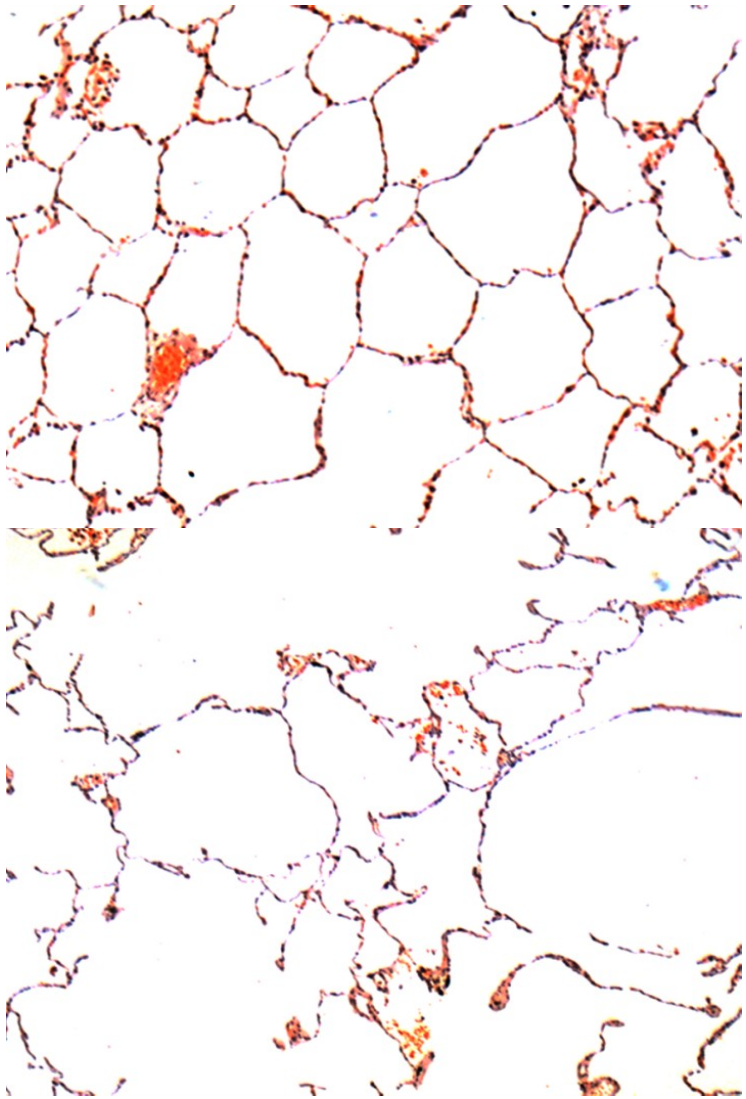
- Centrilobular 25%
- Centrilobular+Paraseptal 31%
- Centrilobular+Paraseptal+ Pablobular 18%
- Centrilobular+Panlobular 8%
- Panlobular 3%
- Paraseptal 15%

Centrilobular emphysema



Panlobular emphysema

Normal



Emphysema

Emphysema Histology

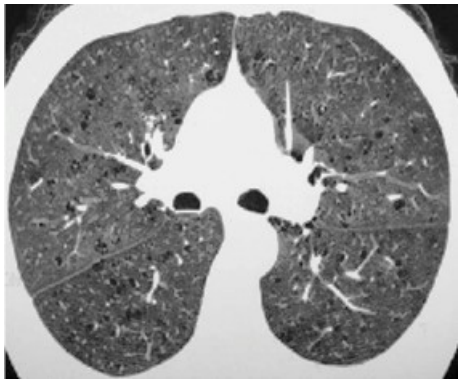
Histology is non-specific

Large empty spaces

Brocken alveolar walls

With or without inflammation

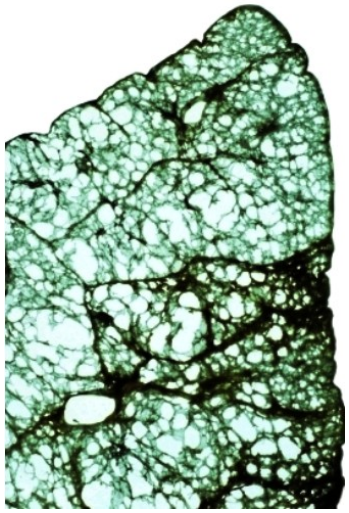
With or without fibrosis



Centrilobular emphysema
Most common type

US prevalence is around **13 million cases**.

Among **white male smokers, 14% are affected,** while **3% of white male nonsmokers develop the disease**



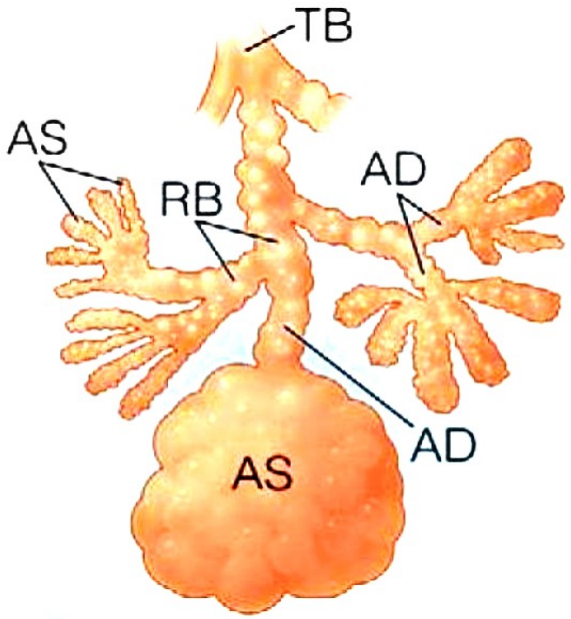
Panlobular emphysema
Least common type

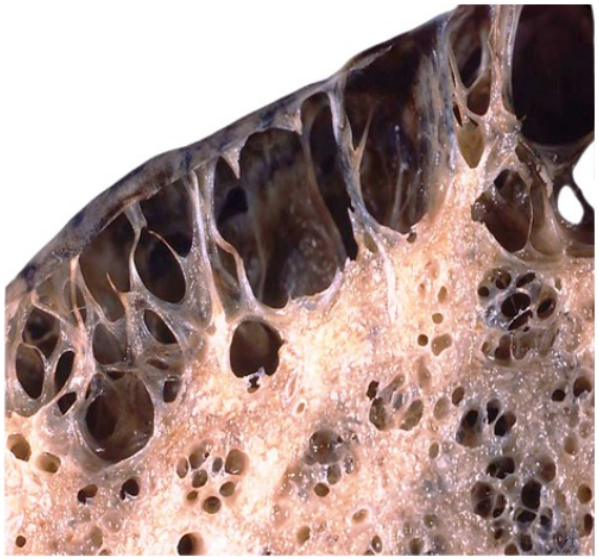
US prevalence is estimated to be around **500,000 cases.**

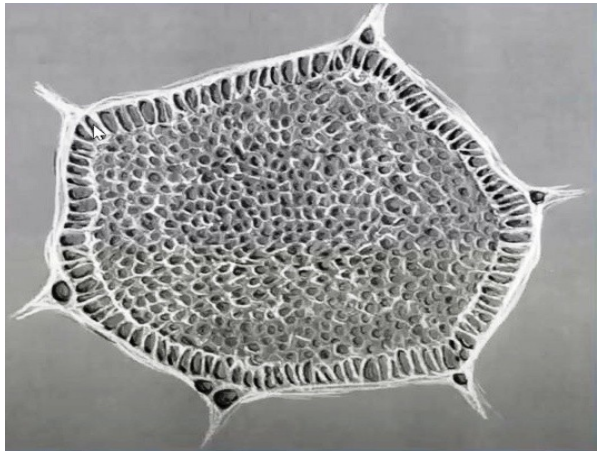
Linked to **alpha-1 antitrypsin deficiency,** smoking and occupational exposure to **dust and fumes, air pollution** and certain **drug** use (like Ritalin)

Number of patients with alpha-1 antitrypsin deficiency in the US is about 100,000

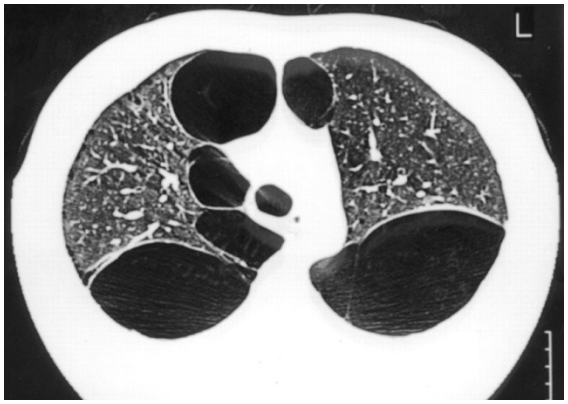
Paraseptal (distal acinar) emphysema

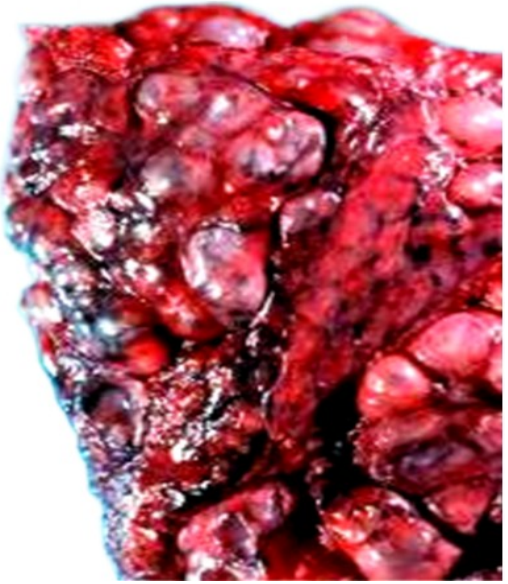


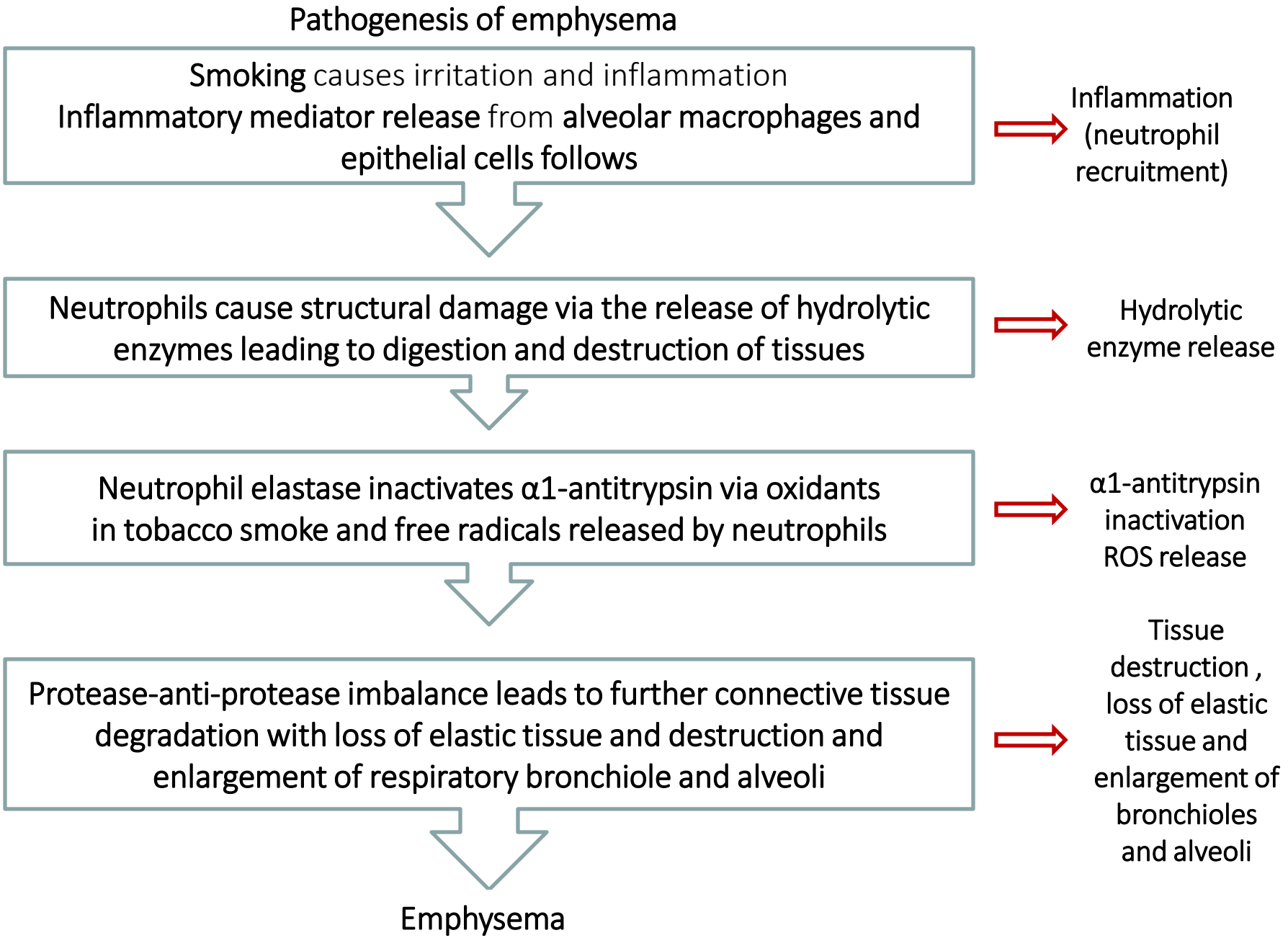




Bullous Emphysema



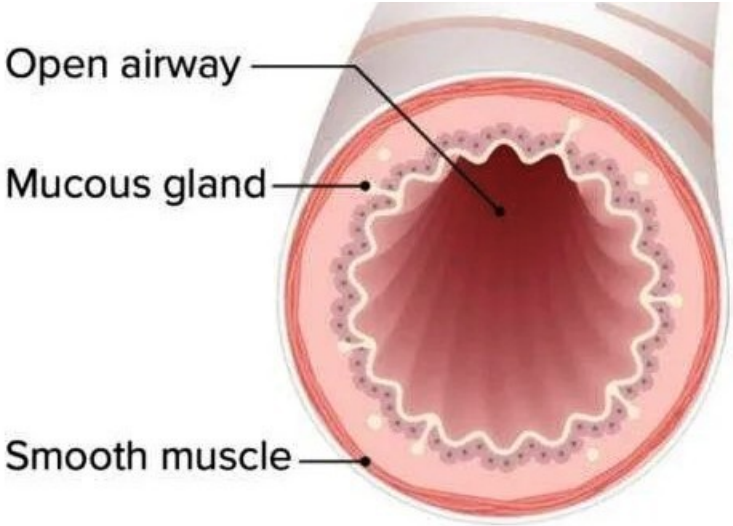


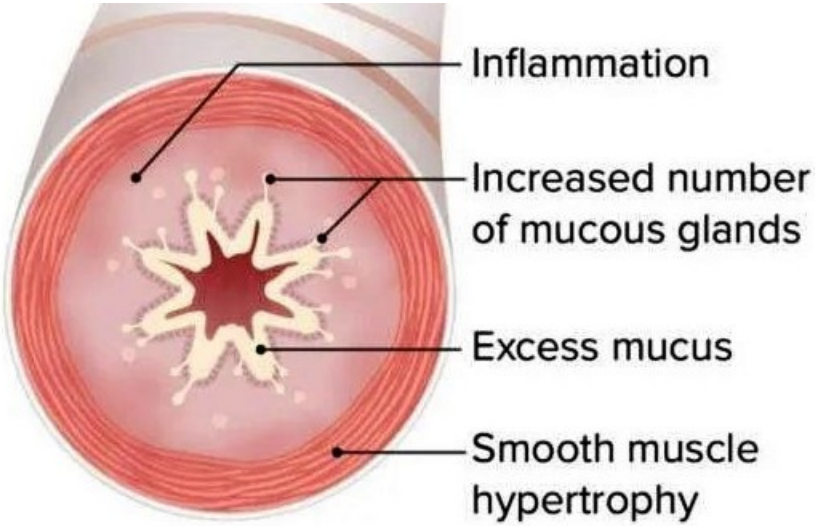

Pathogenesis of emphysema
Smoking causes irritation and inflammation
Inflammatory mediator release from alveolar macrophages and epithelial cells follows
Inflammation (neutrophil recruitment)
Neutrophils cause structural damage via the release of hydrolytic enzymes leading to digestion and destruction of tissues
Hydrolytic enzyme release
Neutrophil elastase inactivates α1-antitrypsin via oxidants in tobacco smoke and free radicals released by neutrophils
α1-antitrypsin inactivation
ROS release
Protease-anti-protease imbalance leads to further connective tissue degradation with loss of elastic tissue and destruction and enlargement of respiratory bronchiole and alveoli
Tissue destruction , loss of elastic tissue and enlargement of bronchioles and alveoli
Emphysema

Chronic bronchitis

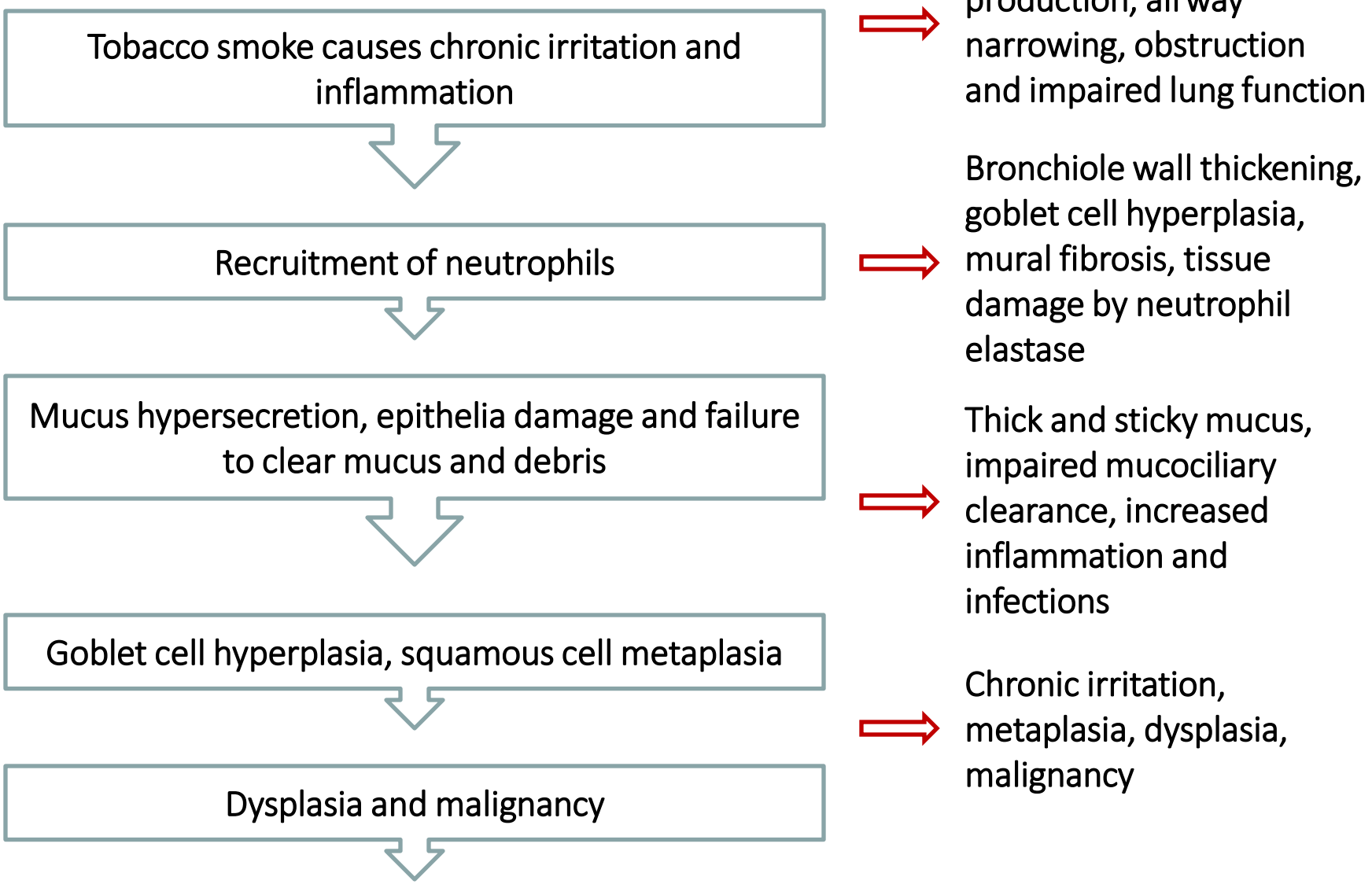
Persistent cough with sputum production for at least 3 months each year in at least 2 consecutive years in the absence of any other identifiable cause

Tobacco smoke leads to irritation of airways, cellular damage, mucus hypersecretion, goblet cell hyperplasia and later metaplasia, bronchiolitis and secondary infections



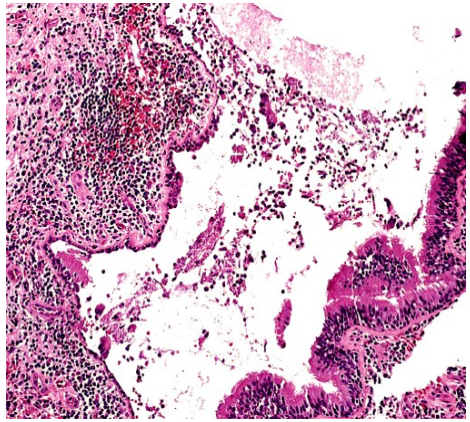


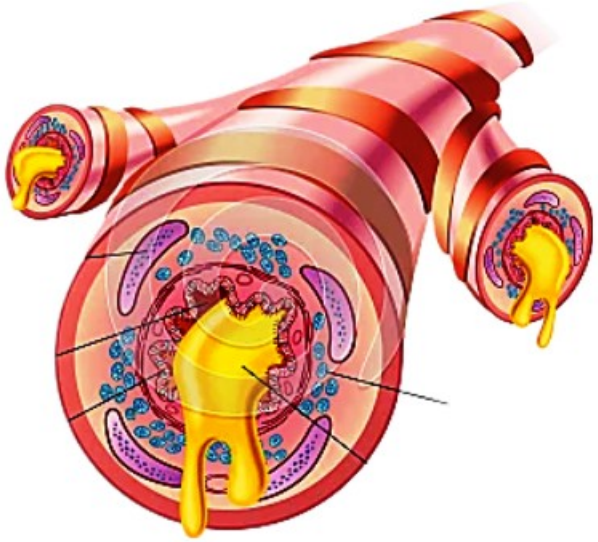
Pathogenesis of chronic bronchitis

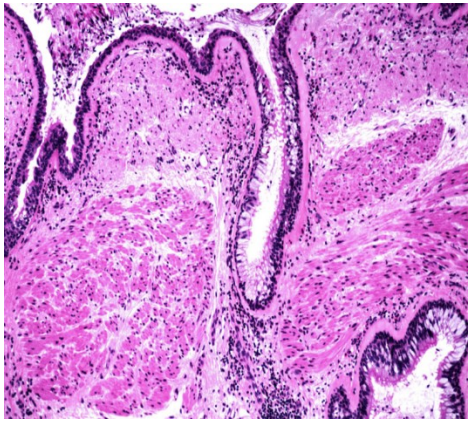

Tobacco smoke causes chronic irritation and inflammation
Excessive mucus production, airway narrowing, obstruction and impaired lung function
Recruitment of neutrophils
Bronchiole wall thickening, goblet cell hyperplasia, mural fibrosis, tissue damage by neutrophil elastase
Mucus hypersecretion, epithelia damage and failure to clear mucus and debris
Thick and sticky mucus, impaired mucociliary clearance, increased inflammation and infections
Goblet cell hyperplasia, squamous cell metaplasia
Chronic irritation, metaplasia, dysplasia, malignancy
Dysplasia and malignancy
Cancer

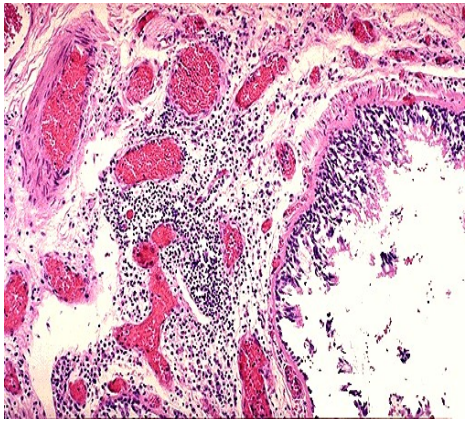
Pathogenesis of chronic bronchitis Tobacco smoke causes chronic irritation which can lead to inflammation, excessive mucus production, airway obstruction and impaired lung function
Release of inflammatory mediators Cytokines (TNF-α, IL-1β and IL-8) Chemokines (Chemoattractants CCL2, 3, 5 8, 10) Reactive Oxygen Species (ROS)
Mucous gland hypertrophy with increased mucus secretion
Disruption of the ciliary action of the respiratory epithelium
CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene dysfunction due to smoking, inflammation or infection
Infection by S. pneumoniae, H. influenzae and Moraxella catarrhalis
Goblet cell metaplasia
Squamous dysplasia
Carcinoma

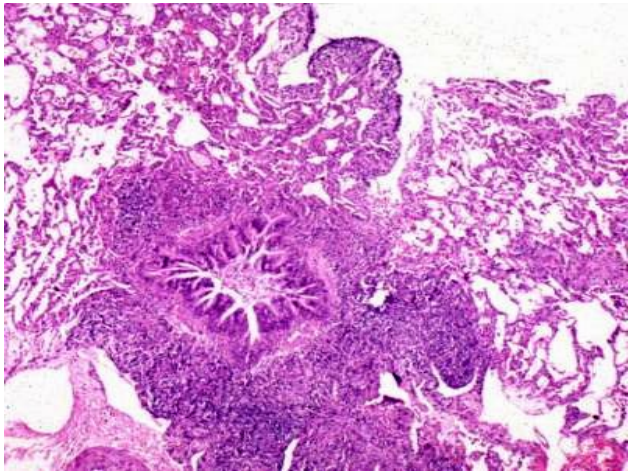
Chronic bronchitis

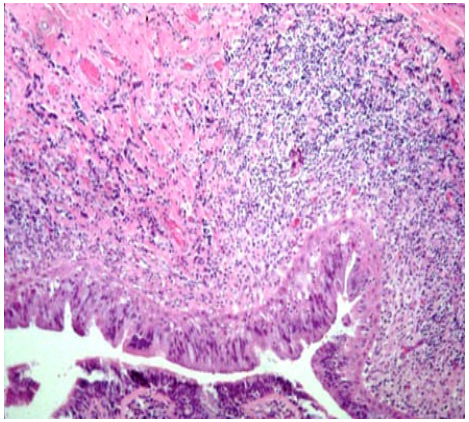












Morphology

Hyperemia and edema of mucosa

Mucus hypersecretion and bronchial narrowing by mucus casts

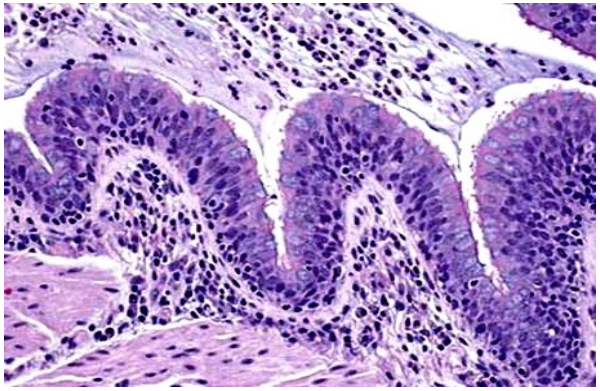
Increased mucus gland size

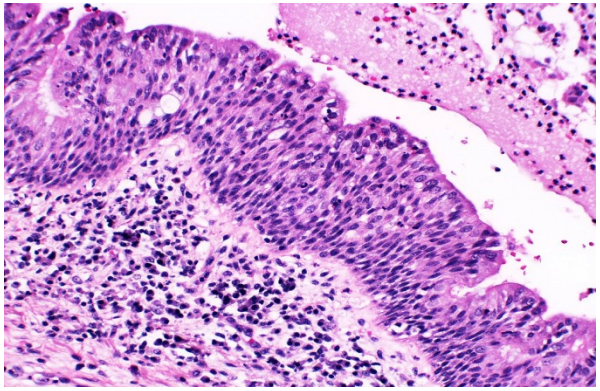
Inflammation and fibrosis of small bronchi and bronchioles

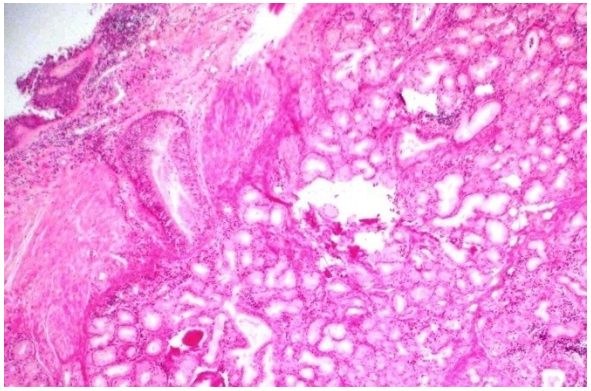
Squamous metaplasia

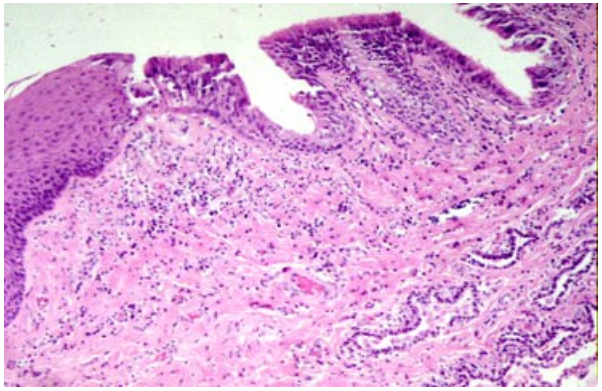
Squamous dysplasia

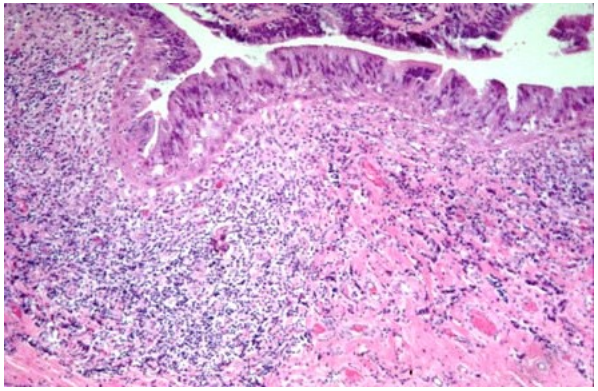
Carcinoma

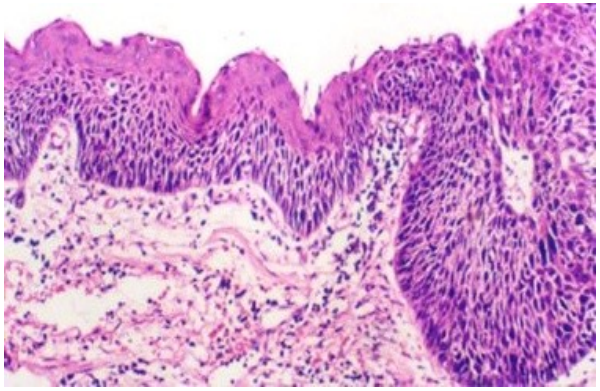




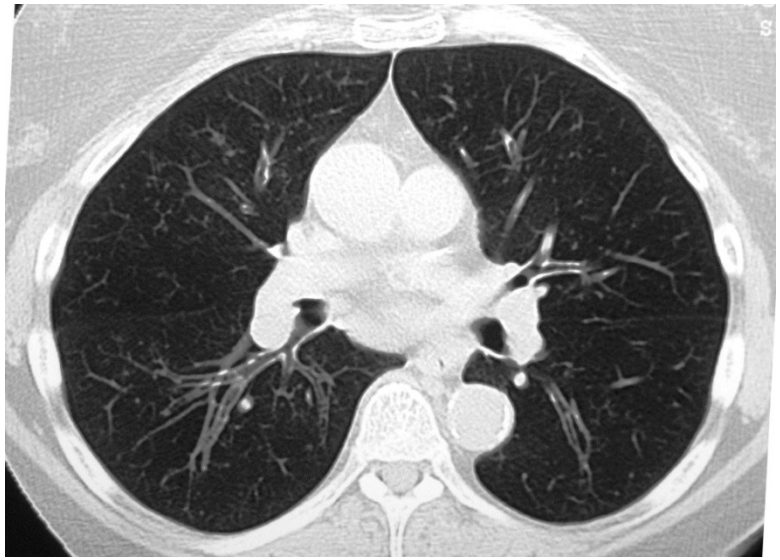


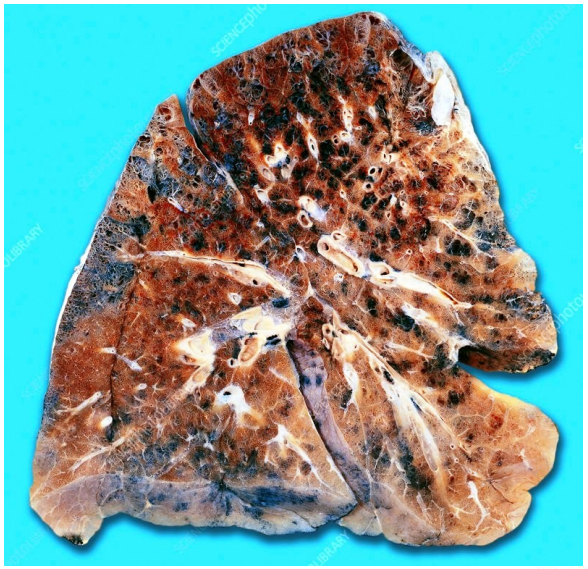


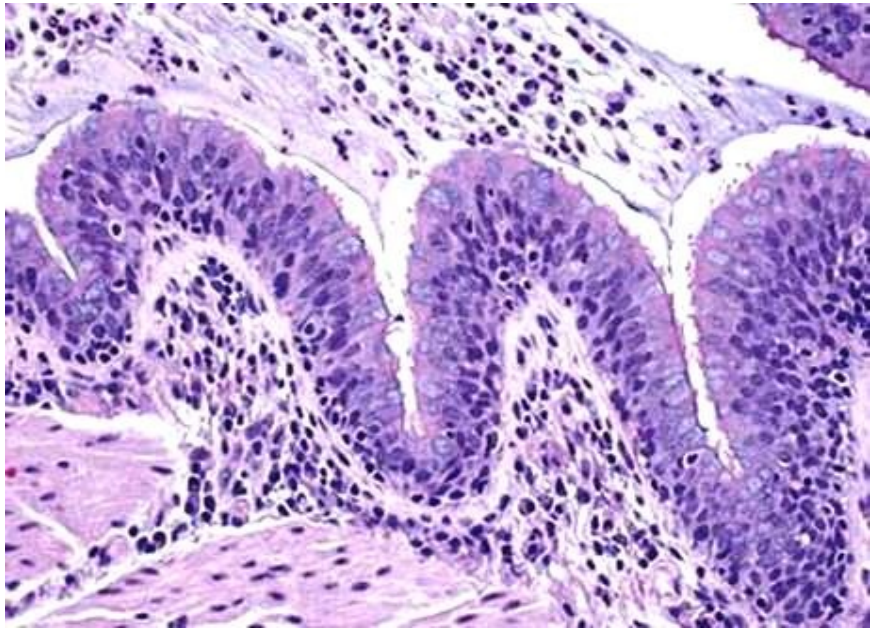


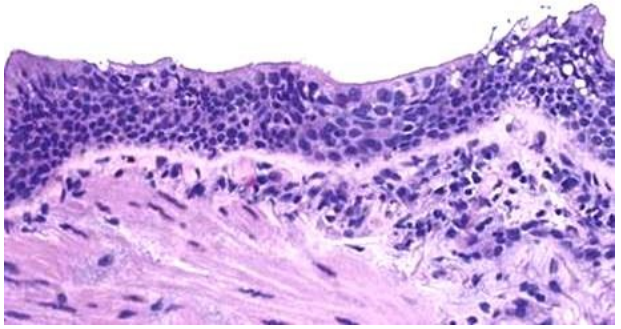


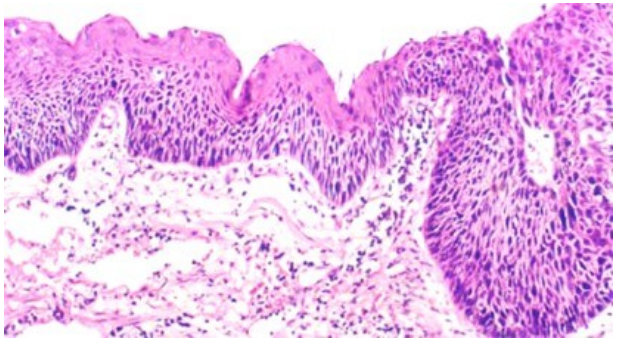
Chronic bronchitis with squamous metaplasia amd dysplasia











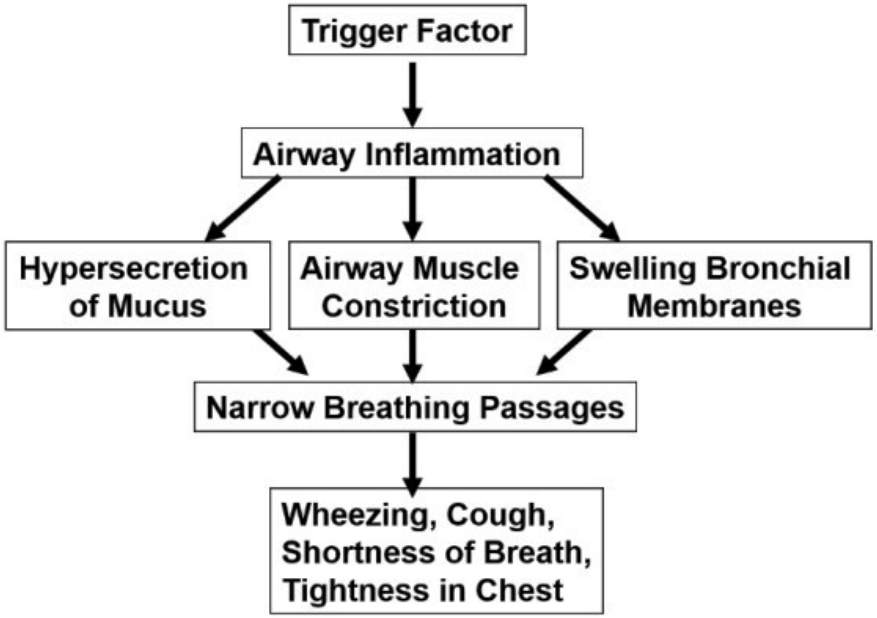
Predominant features of chronic bronchitis and emphysema		
	Chronic bronchitis	Emphysema
Age (years)	40-45	50-75
Dyspnea	Mild, late	Severe, early
Cough	Early, copious sputum	Late scant sputum
Infections	Common	Occasional
Respiratory insufficiency	Early, periodic	End stage
Cor pulmonale	Common	Uncommon, end stage
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels, large heart	Hyperinflation, normal heart
Chest CT	Bronchial wall thickening, often described as a "dirty chest" with increased lung markings, thickening of small airways	Areas of low attenuation (darker areas) due to air trapping and tissue destruction, bullae
Clinical appearance	Blue bloater	Pink buffer

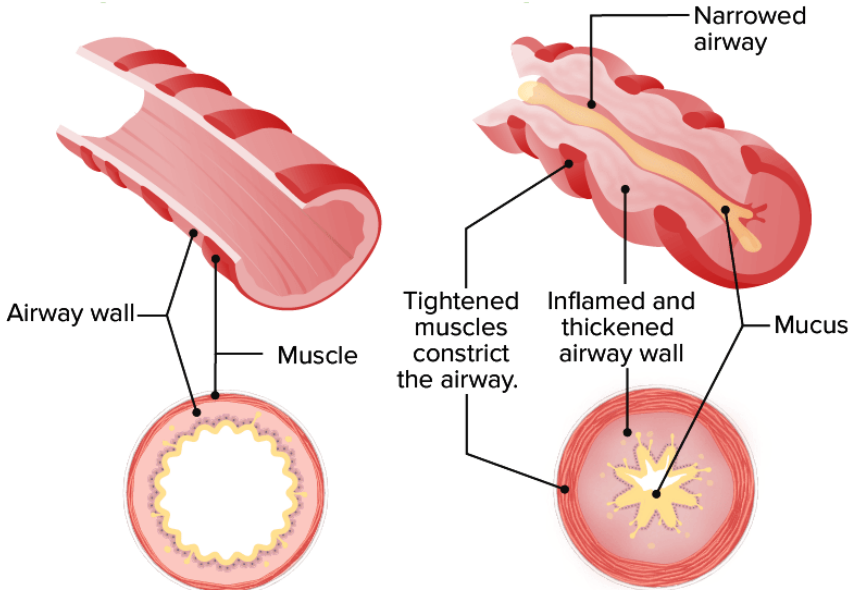
Asthma

Chronic relapsing inflammatory disorder
- Paroxysmal reversible bronchospasm
- Smooth muscle hyper-reactivity
- Increased mucus production
- Inflammation (eosinophilic or neutrophilic)

Heterogeneous with variable phenotypes

Categorized by underlying triggers
- Atopic (allergic)
- Non-atopic
- Drug-induced
- Occupational
- Mixed





Types of asthma	
Atopic (allergic) asthma	IgE-mediated type I hypersensitivity reaction Antigens include dust, pollen, certain foods, etc Positive family history of atopy T helper type 2 high (Th2 high) Eosinophilic airway inflammation Eosinophils
Non-atopic asthma	Hyper-irritability of airways Causes include infections, chemical irritants, exercise, cold exposures, etc No a family history of atopy T helper type 2 low (Th2 low) Neutrophilic airway inflammation Neutrophils
Drug-induced asthma	Pharmacological agents with aspirin and other NSAIDs Inhibition of the cyclo-oxygenase (COX) pathway Overproduction of bronchoconstrictor leukotrienes ⇩ COX ⇧ LOX
Occupational asthma	Fumes (epoxy resins, plastics), organic and chemical dusts (wood, cotton, platinum), gases (toluene), other chemicals (formaldehyde, penicillin products). Underlying mechanisms vary according to stimulus Allergic reactions, direct release of bronchoconstrictors, hypersensitivity responses of unknown origin, other mechanisms

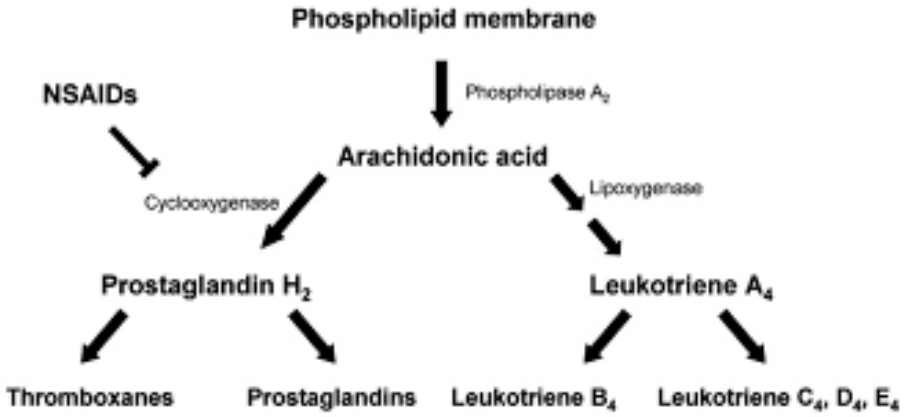
NSAID-induced asthma, also known as Aspirin-Exacerbated Respiratory Disease (AERD)

Inhibition of the COX2 enzyme

Shift in arachidonic acid metabolism, diverting it towards the lipoxygenase (LOX) pathway

Increased production of leukotrienes (Cys-LTs)

LTs are potent bronchoconstrictors



Leukotrienes	Prostaglandins
Eicosanoids produced by **leukocytes**	Eicosanoids produced by **all cell types**
Generated from arachidonic acid by **Lipoxygenase (LOX)**	Generated from arachidonic acid by **cyclo-oxygenase (COX)**
Allergic reaction & sustained inflammatory responses	Vasodilatation, smooth muscle regulation and inflammation

Asthma

Current classification is based on the status of Th2 inflammation

Th2-high asthma

Eosinophilic airway inflammation
Associated with increased blood eosinophil counts
Elevations of Fractional Exhaled Nitric Oxide (FeNo)

Th2-low asthma

Neutrophilic asthma

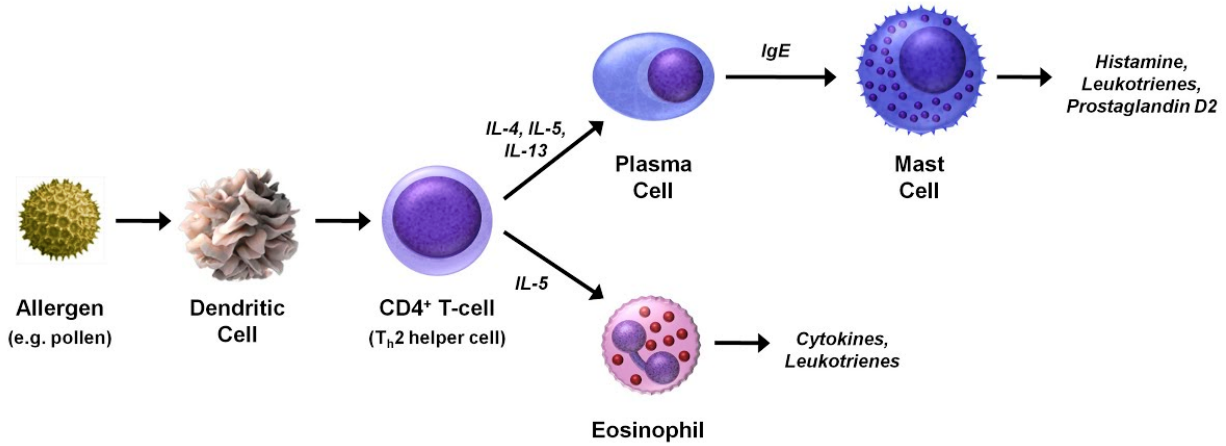
Mixed asthma

Coexistence of eosinophilic and neutrophilic airway inflammation is considered mixed asthma

CD4+ T (helper) T cells Several subtypes based on cytokine production and functions	
Th1 cells	Involved in cell-mediated immunity Produce cytokines like IFN-γ and IL-2 to fight intracellular pathogens, viruses and tumor antigens
Th2 cells	Play a crucial role in humoral immunity Produce cytokines like IL-4 and IL-13 to stimulate B cells for antibody synthesis, particularly IgE and activate eosinophils.
Th17 cells	Important in defending against extracellular pathogens Produce cytokines like IL-17 and IL-22
Treg cells (Regulatory T cells)	Maintain immune homeostasis and prevent autoimmunity by suppressing immune responses.
Tfh cells (Follicular Helper T cells)	Help B cells in germinal centers to produce antibodies
Th9 cells	Distinguished by their production of IL-9 upon activation
Th22 cells	Produce IL-22 and have been implicated in a range of autoimmune disorders

Th2 High Asthma

Allergens recognition by dendritic cells → Th2 helper cell activation and cytokine release → Interleukins stimulate B cell to produce IgE → Mast cells degranulation and histamine release → Bronchospasm and eosinophil recruitment → Inflammation and MBP release → Acetylcholine release → Inflammation and bronchospasm → Asthma



IL-13 directly sensitizes airway **smooth muscle contraction**, stimulates epithelial cells to secret **mucins** and induces **fibrosis**

Asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, atopic dermatitis (eczema), allergic contact dermatitis, etc

Th2 Low Asthma

Bacteria recognized by dendritic cells

⬇

Th17 activation and Th1 cell stimulation

⬇

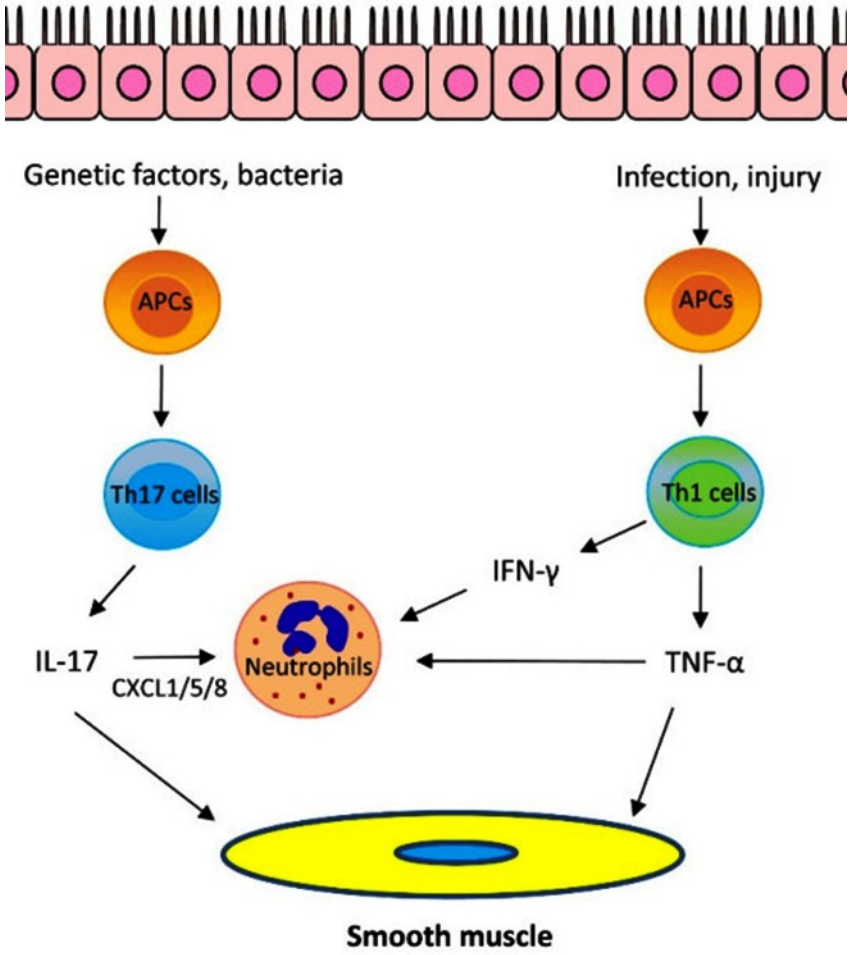
Epithelial cells and fibroblasts activation with chemo-attractant and cytokine release

⬇

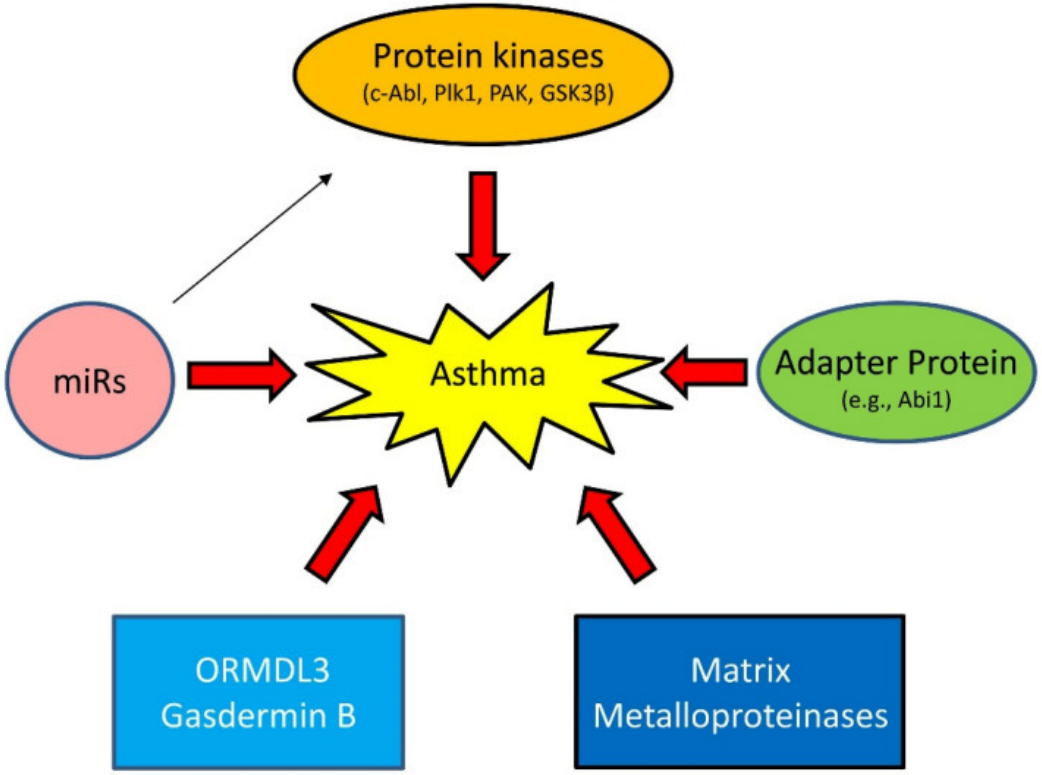
Neutrophil recruitment and smooth muscle contraction

⬇

Cytokines (IFN-γ and TNF-α) upregulate Ca^{2+} signaling in airway smooth muscle and induces airway hyper-responsiveness (AHR)



inflammation-independent (protein driven) asthma



ORMDL3 stands for Orosomucoid-like 3

Asthma has long been viewed as an inflammatory disease

Emerging evidence suggests that **inflammation-independent** processes also contribute to asthma progression

Protein driven asthma proteins like **kinases, adapter protein, matrix metalloproteinases and others, drive asthma progression.**

Th2-High-Related Biomarkers	
Eosinophil count in sputum or blood	Increased **sputum eosinophil levels (>3%)** have been associated with high airway inflammation, frequent asthma exacerbation and poor asthma control Relationship between blood and sputum eosinophil counts Not a specific marker of Th2 lower airway inflammation
Serum IgE	IgE plays a key role in the **pathogenesis of allergic asthma** (elevated levels of IgE are correlated with patients with asthma)
Nitric Oxide	**Produced by epithelial cells** as a result of IL-13-induced **upregulation of nitric oxide synthase** in the airway epithelium and is, **specific marker of Th2 airway inflammation** (Fractional exhaled nitric oxide or **FeNO**)
Cytokines	**Levels of IL-4, IL-5, and IL-13** in sputum and BALF are higher in asthmatics. **Thymic stromal lymphopoietin** (TSLP), IL-33, and IL-25 in epithelium are elevated in asthmatic patients. These cytokines are the **gold standard** to verify Th2-high asthma for clinical research
Periostin	**Surrogate marker of Th2 inflammation** and serum periostin levels are significantly **higher in asthmatic patients with eosinophilic airway inflammation**

Th2-Low-Related Biomarkers

Clinically late-onset asthma in middle-aged females, obesity, smoking, infection and ozone-associated asthmas

Poor response to inhaled and oral corticosteroids

Classed as **neutrophilic**

Sputum neutrophil count increased because **IL-17 promotes neutrophilic inflammation**

TNF-α and IFN-γ contribute to the **progression** of Th2-low asthma

High levels of IL-6 and CRP have been **linked to severe asthma**

Mediators involved in early and late phases of Asthma	
Early Phase	**Late Phase**
Histamine released by mast cells and basophils causes Rapid bronchoconstriction Increased vascular permeability Mucus secretion Immediate asthma symptoms Leukotrienes Released by mast cells Potent bronchoconstrictors (airway narrowing and inflammation) Prostaglandin E2 Mast cell-derived mediator Induces bronchoconstriction and eosinophil recruitment	Cytokines released by T helper cells (Th2 cells) and other immune cells drive **Eosinophil maturation and activation** (IL-5) Promote **IgE production** (IL-4) Contribute to airway remodeling and mucus production (IL-13) Chemokines Attract eosinophils and other inflammatory cells Perpetuating the inflammatory response Eosinophil-derived proteins (MBP) Released by activated eosinophils Cause epithelial damage and airway hyperresponsiveness
Main mediators **Primary (cytokines, vasoactive amine)** **Secondary (chemokines, ROS, PGs, LTs)**	**Main mediators** **Interleukins 3 and 4** which attract eosinophils **GM-CSF** which recruit neutrophils

Pathogenesis of asthma

Exposure to antigen

T helper T cells (Th2) response

IgE production by plasma cells

Eosinophil recruitment

Re-exposure to antigen

IgE binding to receptors on mast cells

Release of preformed mediators that directly and via neuronal reflexes induce bronchospasm, increased vascular permeability, mucus production and recruitment of leukocytes

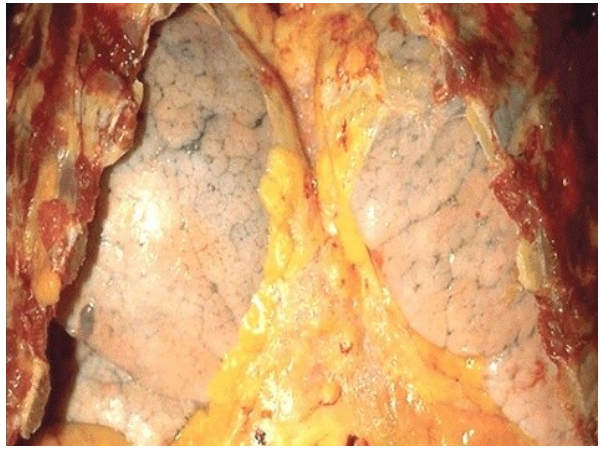
Early-phase reaction

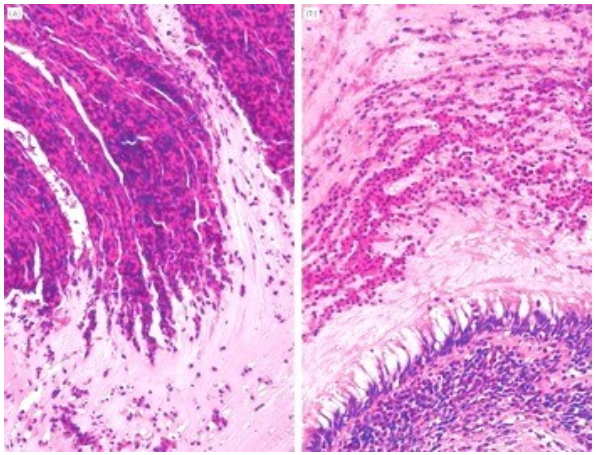
Bronchoconstriction, increased mucus production, variable degrees of vasodilatation and increased vascular permeability

Late-phase reaction

Recruitment of leukocytes (eosinophils, neutrophils, more T cells)

Th17 (IL-17 producing) cells recruit neutrophils.



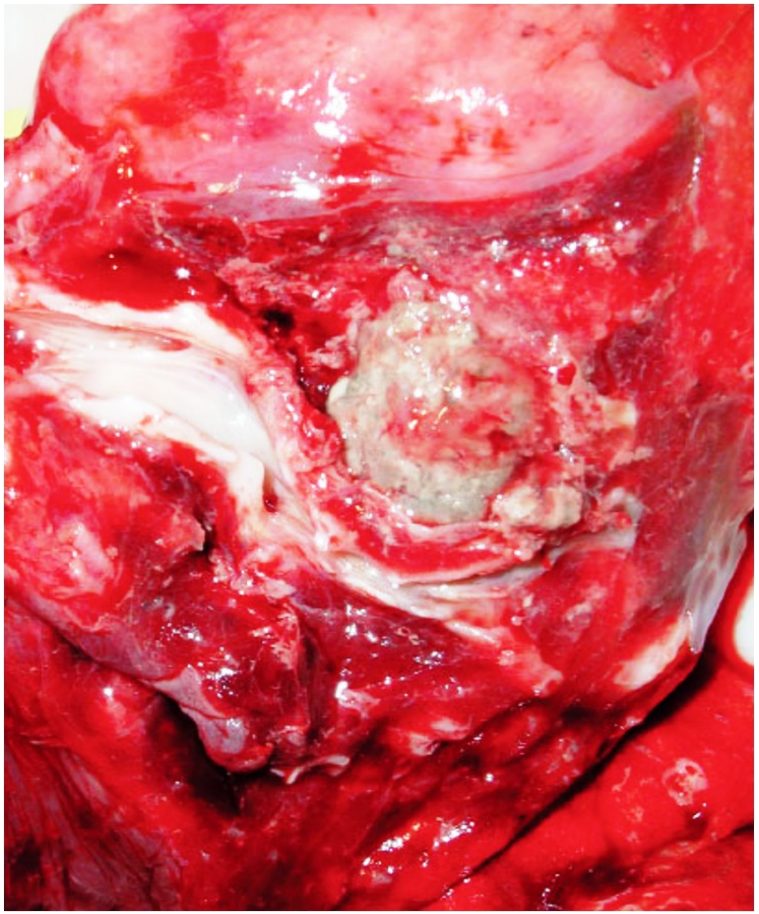


Morphology

Lungs are overinflated

Patchy atelectasis

Mucus plugging of airways.



Asthma on imaging

Bronchial Wall Thickening

Indicates inflammation and remodeling of the airways.

Air Trapping

Due to the obstruction of airflow.

Bronchiectasis

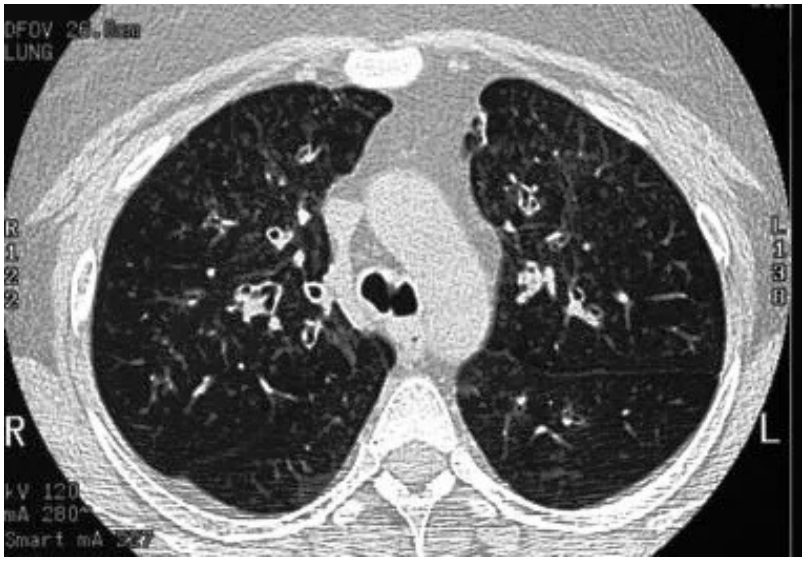
Can be seen in long standing asthma with chronic inflammation.

Emphysema

Can be associated with long-standing or severe asthma, causing a loss of lung tissue and increased lung volume.

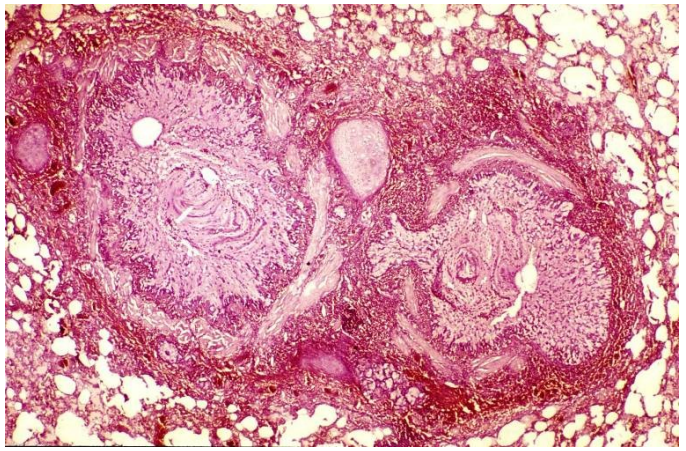
Other Findings:

HRCT can also reveal other changes like reduced airway luminal area, mucoid impaction, centrilobular opacities, and mosaic lung attenuation



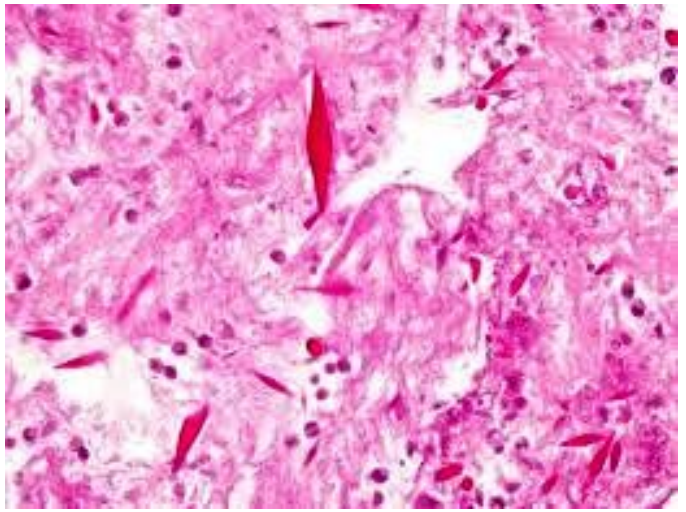
Asthma morphology

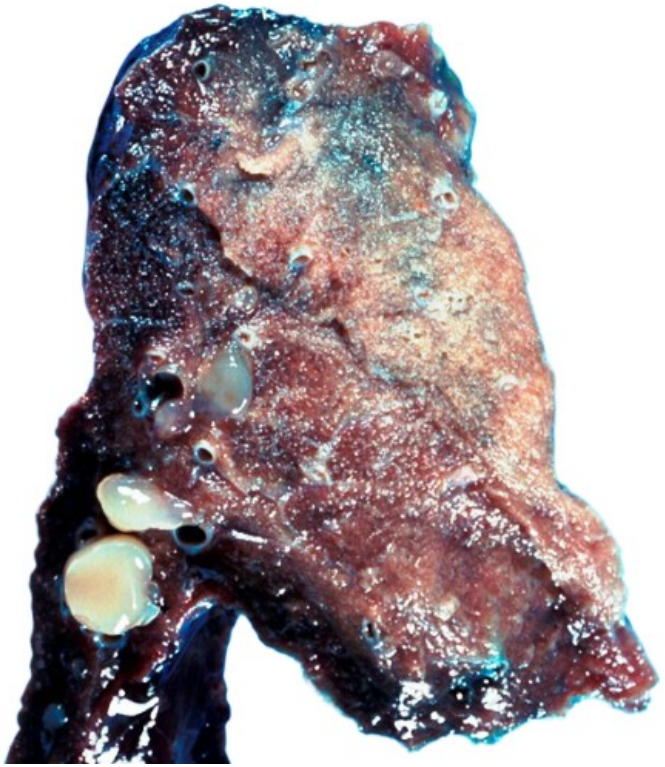
Lungs exhibit **edema, bronchiolar inflammatory infiltrates with numerous eosinophils, subepithelial fibrosis, and bronchial wall smooth muscle and mucosal gland hypertrophy.**

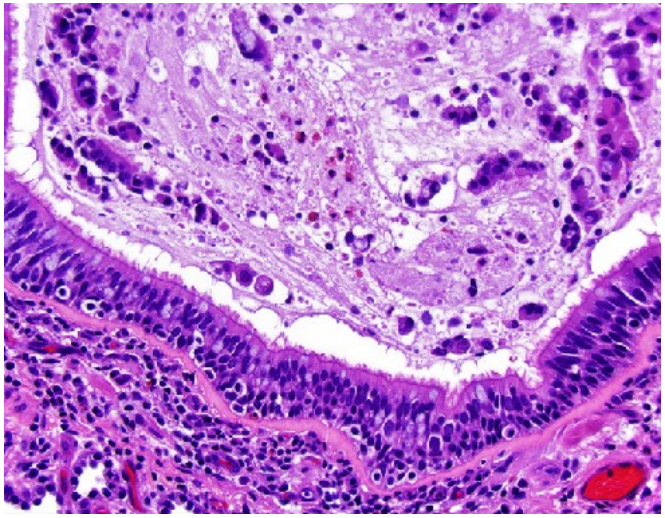


Whorled mucus plugs **(Curschmann spirals)** and crystalloid eosinophil granule **debris (Charcot-Leyden crystals)**, composed of galectin-10 and deposited in airways.

Repeated bouts cause airway remodeling with bronchial smooth muscle and **mucus gland hypertrophy and hyperplasia, increased vascularity, and increased deposition of subepithelial collagen**.







Pathology

Mucus in the lumen

Basement membrane thickening

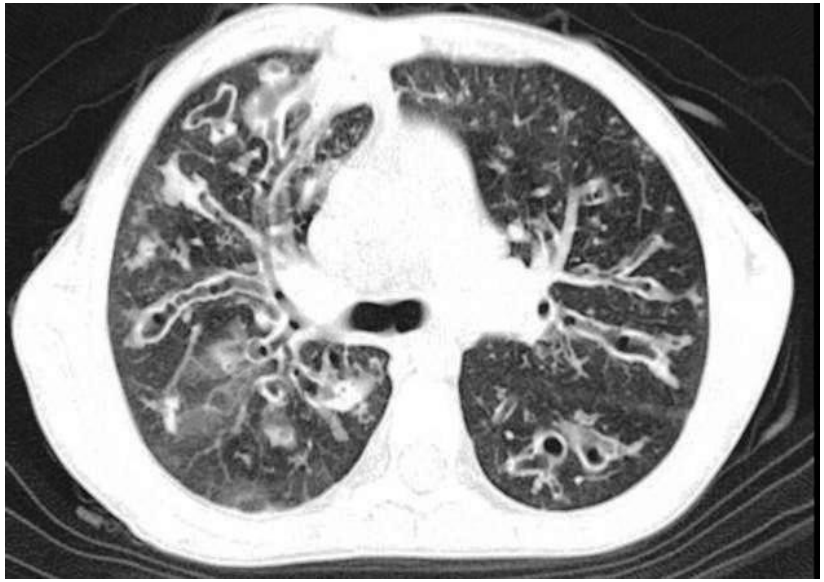
Mural inflammation

Mucous glad hyperplasia

Muscular hypertrophy

Mucus plugs (Curschmann spirals)

Crystalloid eosinophil granule debris (Charcot-Leyden crystals, composed of Galectin-10) deposit in airways



Bronchiectasis

Abnormal **permanent dilation of bronchi and bronchioles**

Caused by **destructive, necrotizing infections of the airways**

Results from **obstruction, infection, tissue destruction, recurrent or severe infection with tissue destruction**

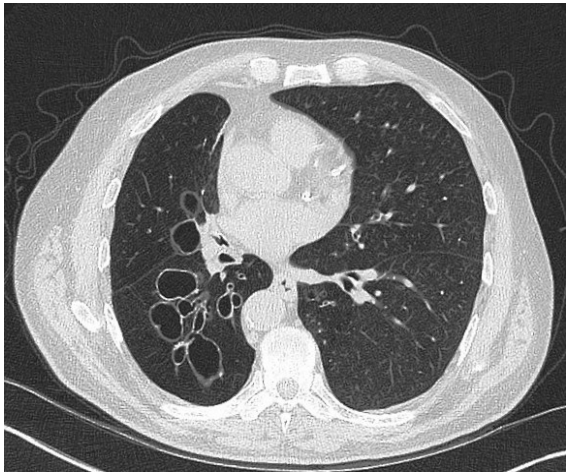
Predisposing factors include sever infections (bacterial pneumonia or viral infection), autoimmune conditions, COPD, asthma, tuberculosis, fungal infections and genetic disorders

Post-infective bronchiectasis follows severe respiratory viral infection or pneumonia

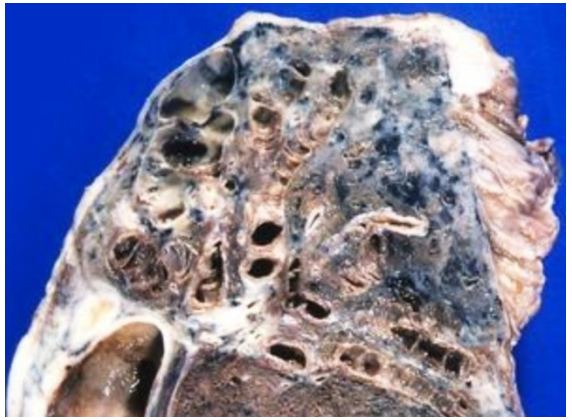
Cause remains **unknown in almost 50%**

Bronchiectasis

Lung damage from bronchiectasis is **irreversible** and treatment options are scarce



Accompanying comorbidities
- Asthma in 50% (ACOS)
- COPD in 36% (BCOS)



Mucociliary dysfunction

Mucus hypersecretion

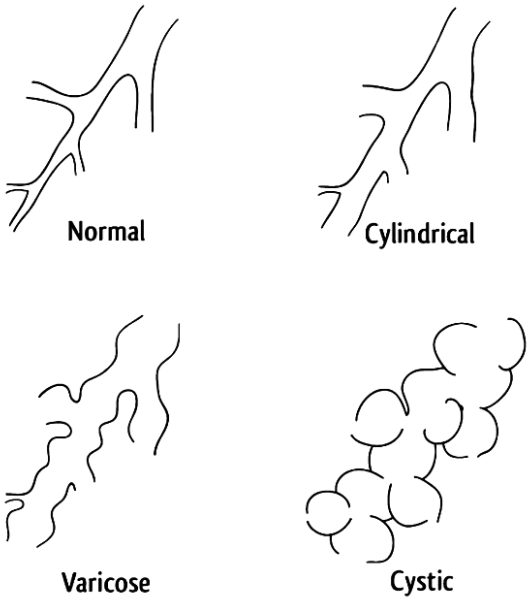
Bronchial obstruction

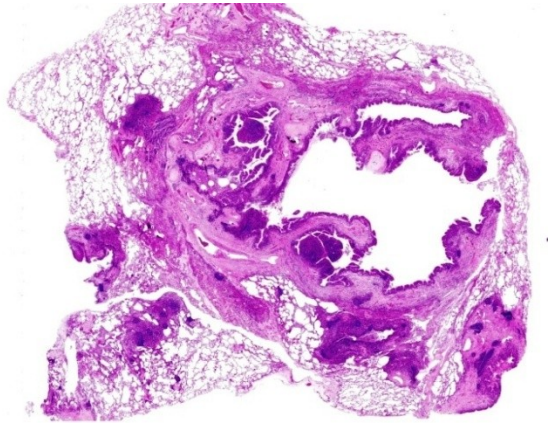
Microbial colonization

Infection

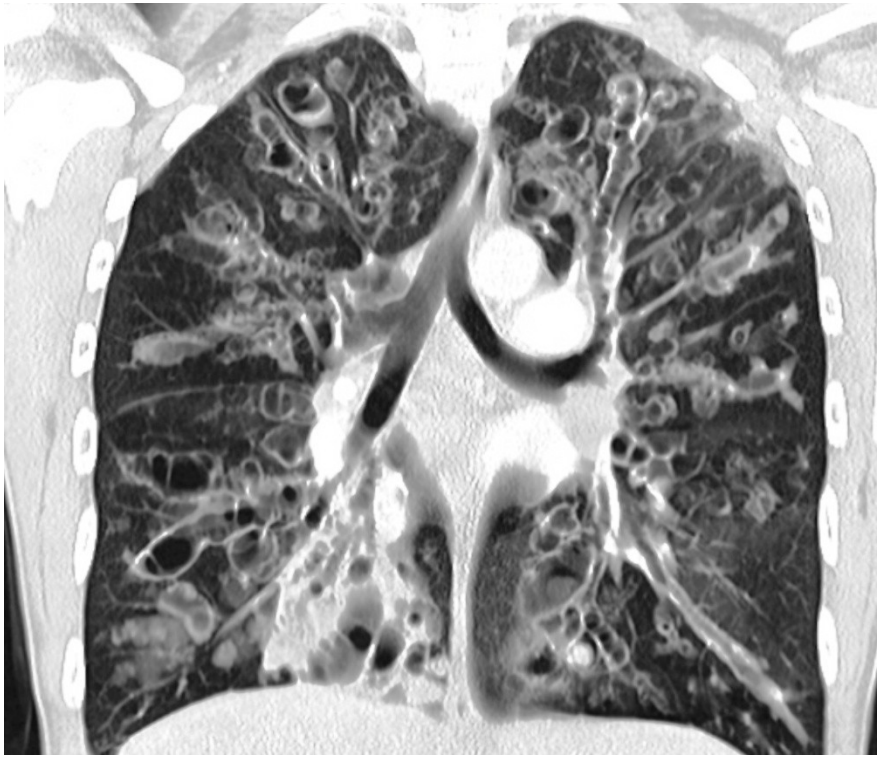
Bronchial destruction

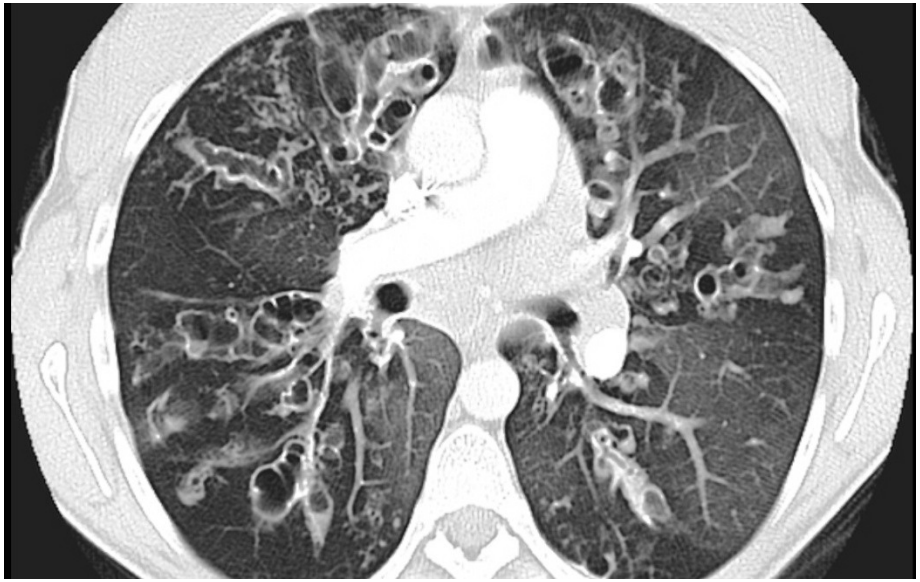
Bronchial dilatation

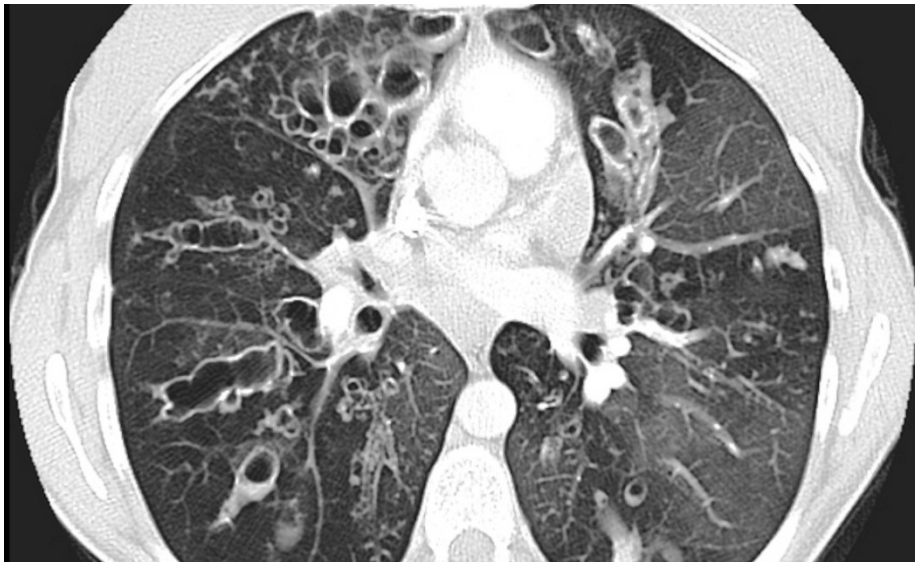


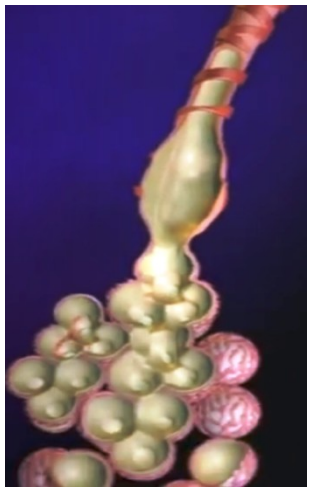


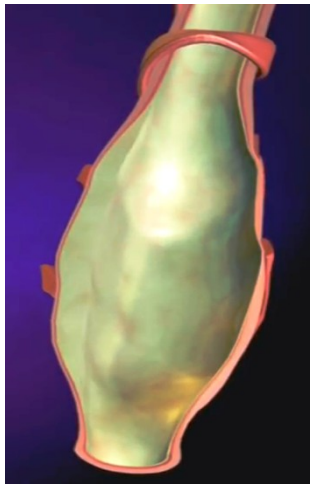
Bronchiectasis



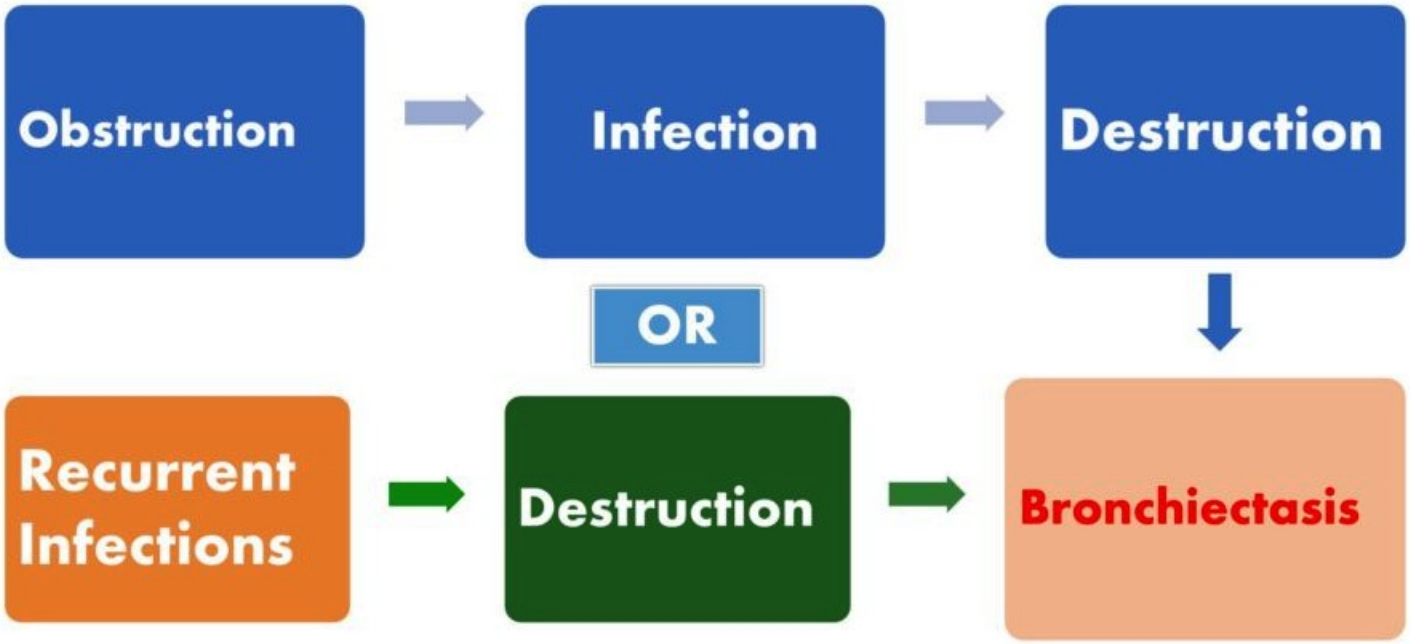






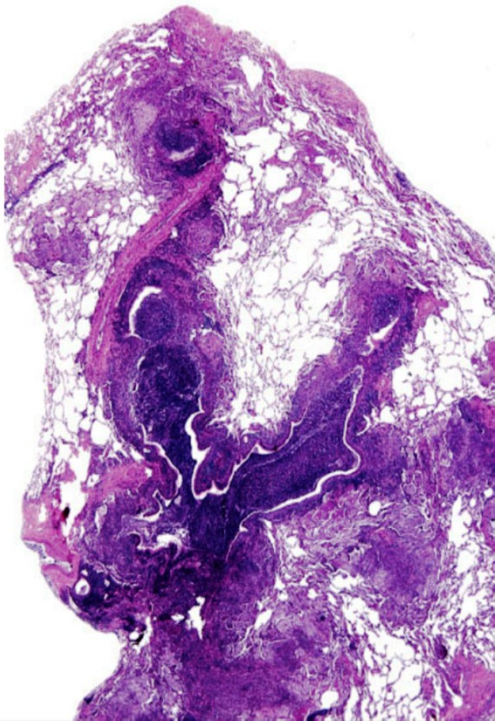


Pathogenesis of Bronchiectasis



Pathology of bronchiectasis
Bronchial dilation
Inflammation
Fibrosis
Mucus impaction
Loss of tissue
Other changes

Bronchiectasis



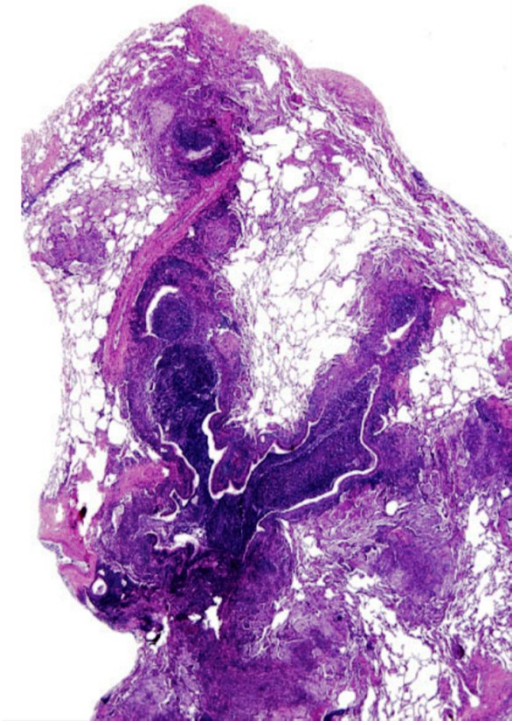
Bronchiectasis

Chronic inflammatory condition

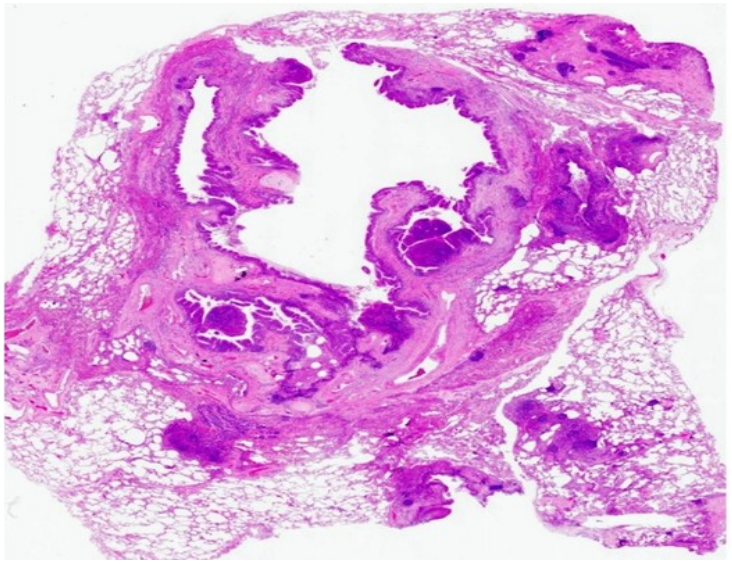
Diverse etiology including recurrent **infections, genetic abnormalities, immunodeficiency and autoimmune disorders**

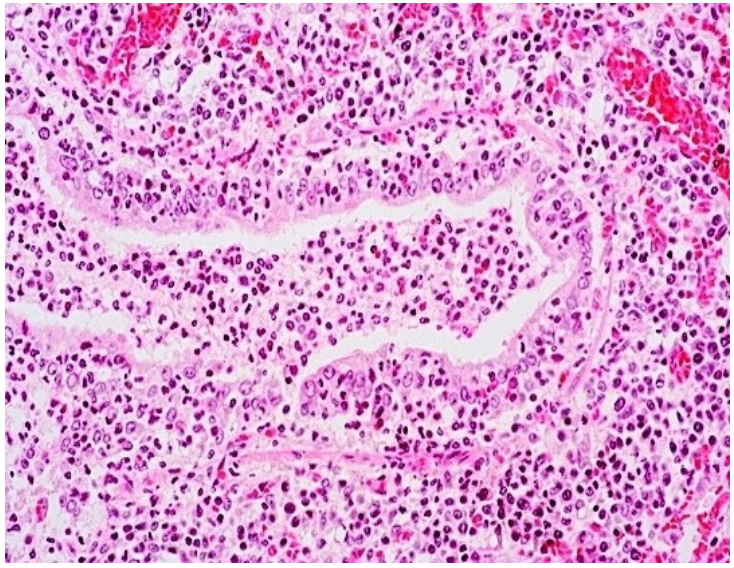
Infection, inflammation, and structural lung damage, often resulting in a **vicious cycle of damage and infection** are the main contributing factors

Mechanisms that can lead to the development of bronchiectasis **are recurrent infections, airway obstruction, peribronchial fibrosis**

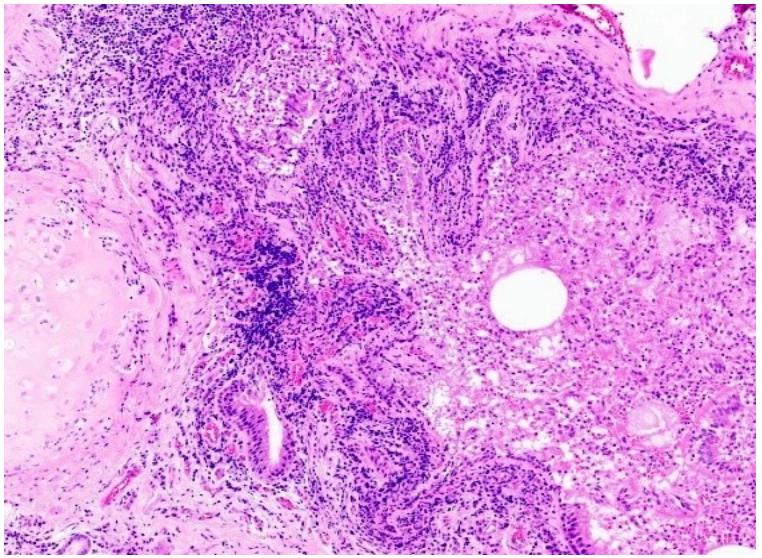


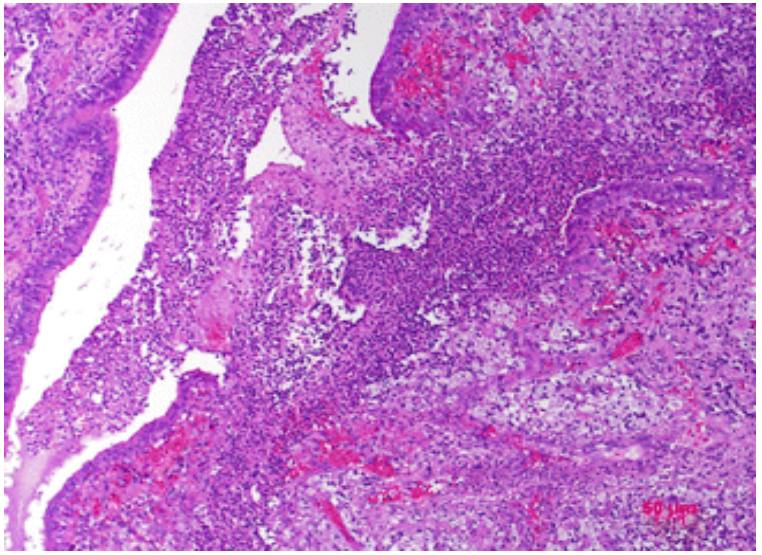
Bronchiectasis





Morphology of bronchiectasis





Morphology

Most severe changes occur in **lower lobes peripherally** with airways dilatation up to 4 times normal size.

Histology shows a spectrum of **mild-to-necrotizing acute and chronic inflammation** of the larger airways with **bronchiolar fibrosis, with squamous metaplasia** that further worsens mucociliary clearance.

Haemophilus influenzae is found in 50% and **Pseudomonas aeruginosa** in 25% of sputum cultures

Complications include **cor pulmonale, brain abscesses, and amyloidosis**

Do not try this at home or anywhere else!